

Rec'd PCT/PTO 01 SEP 2004

REC'D 17 APR 2003

WIPO PCT

10/506459

P1 989698

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 08, 2003

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: 60/362,245

FILING DATE: March 05, 2002

RELATED PCT APPLICATION NUMBER: PCT/US03/05050



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

W. Montgomery
W. MONTGOMERY
Certifying Officer

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

03-07-02

A1/KR1

Modified PTO/SB/16 (6-95)

Approved for use through 04/11/98. OMB 0651-0037

Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

Docket Number P-15654

Type a plus sign (+) inside this box ->

INVENTOR(S)/APPLICANT(S)

LAST NAME	FIRST NAME	MIDDLE NAME	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
ENGLER	THOMAS	ALBERT	Indianapolis, Indiana
CLAYTON	JOSHUA	RYAN	Cicero, Indiana
DIEFENBACHER	CLIVE	G	Indianapolis, Indiana
FURNESS	KELLY	WAYNE	Indianapolis, Indiana
HENRY	JAMES	ROBERT	Indianapolis, Indiana
MALHOTRA	SUSHANT		Indianapolis, Indiana
MARQUART	ANGELA	LYNN	Greenwood, Indiana
McCLAIN	JONATHAN		
MENDEL	DAVID		Indianapolis, Indiana

TITLE OF THE INVENTION (280 characters max)

KINASE INHIBITORS**CORRESPONDENCE ADDRESS**

Eli Lilly and Company
Patent Division/D.C. 1104
Lilly Corporate Center
Indianapolis, Indiana 46285



25885

PATENT TRADEMARK OFFICE

STATE	IN	ZIP CODE	46285	COUNTRY	USA
-------	----	----------	-------	---------	-----

ENCLOSED APPLICATION PARTS (check all that apply)

<input checked="" type="checkbox"/> Specification	Number of pages	100	<input type="checkbox"/> Small Entity Statement
<input type="checkbox"/> Drawing(s)	Number of Sheets		<input type="checkbox"/> Other (Specify)

METHOD OF PAYMENT (check one)

<input type="checkbox"/> A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT (\$)	\$160.00
<input checked="" type="checkbox"/> The Assistant Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 05-0840		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.☐ Yes, the name of the U.S. Government agency and the Government contract number are:Respectfully submitted,
SIGNATURE

Date 3/5/2002

TYPED or PRINTED NAME ROBERT D. TITUS

REGISTRATION NO.
(if appropriate)

40,206

☐ Additional inventors are being named on separately numbered sheets attached hereto**PROVISIONAL APPLICATION FOR PATENT FILING ONLY**

"Express Mail" mailing label number EL832951931 Date of Deposit MAR 5, 2002
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Arlington, VA, 22202.

QUEEN Thomas
Printed Name

Queen Thomas
Signature

03/05/02

03/05/02

KINASE INHIBITORS

BACKGROUND OF THE INVENTION

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase first discovered as one of a number of kinases capable of phosphorylating and inactivating glycogen synthase, the regulatory enzyme of glycogen synthesis in mammals (Embi, et al., Eur. J. Biochem., 107, 519-527 (1980)). Existing in two isoforms, GSK-3 α and GSK-3 β , GSK-3 phosphorylates a wide variety of proteins in vitro. The diversity of these proteins suggests a role for GSK-3 in the control of cellular metabolism, growth, and development.

Type I diabetes is characterized by a lack of insulin resulting from the destruction of insulin producing cells in the pancreas. Type II diabetes is characterized by defective insulin secretion and action. The binding of insulin to its receptor initiates a cascade of events resulting in the phosphorylation and inhibition of GSK-3, contributing to the insulin-induced stimulation of glycogen and protein synthesis. Inhibitors of GSK-3 have been shown to mimic the actions of insulin (Coghlan, et al., Chem. Biol., 7, 793-803 (2000)), including the ability to lower blood glucose levels in vivo (Norman, Drug News Perspect., 14, 242-247 (2001)). These recent discoveries suggest that inhibitors of GSK-3 have a potential role in the treatment of diabetes.

Alzheimer's disease is characterized by the micro-tubule-associated protein Tau existing in an abnormally hyperphosphorylated state (Cohen and Frame, Nature Reviews: Molecular Cell Biology, 2, 769-776 (October 2001) <www.nature.com/reviews/mol-cellbio>). GSK-3 phosphorylates many of the hyperphosphorylated sites on Tau in vitro, preventing it from binding to microtubules, making it available to undergo the aberrant filament assembly that may underlie the neuronal degeneration observed in Alzheimer's disease and other neurological disorders. Inhibitors of GSK-3, such as insulin and lithium

"Express Mail" mailing label number EL832951931 US

Date of Deposit MAR. 5, 2002

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Arlington, VA 22202.

QUEEN Thomas
Printed Name

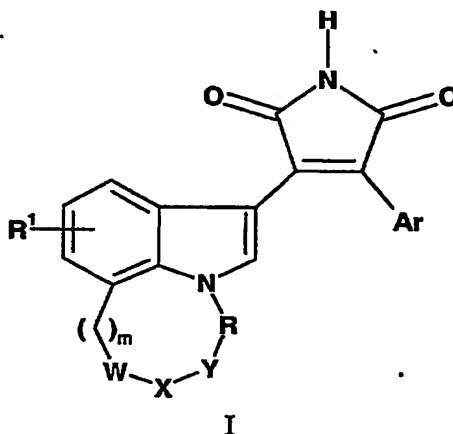
Queen Thomas
Signature

ions, have been shown to induce a partial dephosphorylation of Tau in neuronal cells (Cross, *et al.*, *J. Neurochem.*, 77, 94-102 (2001)). These discoveries suggest that inhibitors of GSK-3 have a potential role in the treatment of degenerative neurological disorders such as Alzheimer's disease.

5 WO 98/16528 describes purine derivatives, WO 99/65897 describes pyrimidine and pyridine derivatives, WO 00/38675 describes maleimides, and WO 01/56567 describes diaminothiazole derivatives that are taught to be inhibitors of GSK-3. Additional GSK-3 inhibitors are necessary to provide treatments for GSK-3 mediated endocrine and neurological disorders. The present invention provides inhibitors of GSK-3.

BRIEF SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I:



15 where:

R^1 is hydrogen, halo, C_1 - C_4 alkyl, or C_1 - C_4 alkoxy;

m is 0, 1, 2, 3, or 4;

R is $-(CH_2)_n-$ or $-CH(OH)-CH(OH)-CH_2-$;

n is 0, 1, 2, 3, or 4;

20 $W-X-Y$ is $-CH_2-CH_2-CH_2-$, $-CH(R^3)-N(R^2)-CH(R^3)-$, or $-CH(R^3)-N(R^4)-C(O)-$;

R^2 is hydrogen, $-(C_1-C_4 \text{ alkylene})-R^5$, C_5-C_7 cycloalkyl, tetrahydropyran-4-yl, $-C(O)R^6$, $-CO_2R^7$, $-CO(NR^8R^9)$, $-SO_2NH_2$, $-SO_2(C_1-C_4 \text{ alkyl})$, or an amino acid residue;

R^3 and $R^{3'}$ are independently selected from the group consisting of hydrogen and C_1 - C_4 alkyl provided that only one of R^3 and $R^{3'}$ may be C_1 - C_4 alkyl;

R^4 is hydrogen or C_1 - C_4 alkyl;

5 R^5 is hydrogen, cyano, phenyl, imidazol-2-yl, -COOH, or -(morpholin-4-yl)carbonyl;

R^6 is hydrogen, C_1 - C_{10} alkyl, pyridinyl, pyrazinyl, morpholin-4-yl, piperazinyl, 1-(C_1 - C_4 alkyl)piperazin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl, 1-(C_1 - C_4 alkoxy-carbonyl)piperidin-4-yl, or $-CH_2-R^{10}$;

10 R^7 is C_1 - C_6 alkyl, 2-methoxyethyl-1-yl, -(C_1 - C_2 alkylene)morpholin-4-yl, or phenyl optionally substituted with one or two substituents independently selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, and trifluoromethyl;

R^8 is hydrogen or C_1 - C_4 alkyl;

R^9 is hydrogen or C_1 - C_4 alkyl;

R^{10} is $-OCH_2CH_2OCH_3$, $-NR^{14}R^{15}$, or morpholin-4-yl;

15 Ar is benzofur-4-yl, benzofur-7-yl, benzothien-4-yl, benzothien-7-yl, 1-(R^{11})benzimidazol-4-yl, 1-(R^{11})indol-4-yl, indol-7-yl, isoquinolin-5-yl, 2,3-dihydrobenzofur-4-yl, 2,3-dihydrobenzofur-7-yl, 1,3-dihydroisobenzofur-4-yl, 1,3-dihydroisobenzofur-5-yl, benzo[1,3]dioxol-4-yl, benzo[1,3]dioxol-5-yl, 2,3-dihydrobenzo[1,4]dioxin-5-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2',2'-difluorobenzo[1,3]dioxol-4-yl, or 2',2'-difluorobenzo[1,3]dioxol-5-yl each optionally substituted in the phenyl ring with substituents R^{12} and R^{13} , or Ar is a group selected from imidazo[1,2-*a*]pyridin-3-yl optionally substituted with cyano, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-3-yl, imidazo[1,2-*a*]pyridin-5-yl, furo[3,2-*c*]pyridin-7-yl optionally substituted with halo or $-NR^{14}R^{15}$, thieno[3,2-*b*]pyridin-7-yl, or pyrazolo[2,3-*a*]pyridin-3-yl;

25 R^{11} is hydrogen, C_1 - C_4 alkyl, or $-(CH_2)_p-G$;

R^{12} is halo, hydroxy, amino, C_1 - C_4 alkoxy, $-NHC(O)(C_1-C_4$ alkyl), or $-O-(CH_2)_p-G$;

R^{13} is halo;

p is 2, 3, 4, or 5;

30 G is hydroxy or $NR^{14}R^{15}$;

R^{14} and R^{15} are independently selected from the group consisting of hydrogen and C_1 - C_5 alkyl; or a pharmaceutically acceptable salt thereof, provided that when n is 0,

W-X-Y is not $-\text{CH}(\text{R}^3)-\text{N}(\text{R}^2)-\text{C}(\text{O})-$.

The present invention further provides a method of inhibiting GSK-3 in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

5 The present invention also provides a method of treating diabetes in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

10 The present invention also provides a method of treating Alzheimer's disease in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

The present invention also provides a pharmaceutical formulation comprising a compound of Formula I, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

15 This invention also provides the use of a compound of Formula I for the manufacture of a medicament for the inhibition of GSK-3. Additionally, this invention provides a pharmaceutical formulation adapted for the treatment of diabetes containing a compound of Formula I. Furthermore, this invention provides the use of a compound of Formula I for the manufacture of a medicament for the treatment of diabetes. This invention also provides the use of a compound of Formula I for the manufacture of a
20 medicament for the treatment of Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

The general chemical terms used in the formulae above have their usual meanings. For example, the term "C₁-C₆ alkyl" includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, neopentyl, and hexyl moieties. The term "C₁-C₄ alkoxy" is
25 taken to mean a C₁-C₄ alkyl group linked to the parent molecule through an oxygen atom, and includes the groups methoxy, ethoxy, isopropoxy, and the like. Likewise, the term "C₁-C₄ alkylthio" is taken to mean a C₁-C₄ alkyl group linked to the parent molecule through a sulfur atom, and includes methylthio, ethylthio, isobutylthio, and the like. The
30 term "halo" includes fluoro, chloro, bromo, and iodo.

The term "(C₁-C₄ alkylene)-R⁵" is taken to mean a linear or branched alkylene chain substituted at any carbon atom with the variable R⁵ and includes, for example, linear or branched alkyl chains, benzyl, and α -methylbenzyl moieties.

The term "amino acid residue" is taken to mean an amino acid moiety selected from the group consisting of alanyl, arginyl, asparaginy, aspartyl, cysteinyl, glutaminy, glutamyl, glycy, histidyl, isoleucyl, leucyl, lysyl, methionyl, phenylalanyl, phenylglycyl, prolyl, seryl, threonyl, tryptophanyl, tyrosyl, and valyl bonded through an acid carbonyl.

The term "GSK-3" is taken to mean GSK-3 α and/or GSK-3 β .

The term "diabetes" is taken to mean Type I and/or Type II diabetes.

The skilled artisan will appreciate that certain compounds of Formula I contain at least one chiral center. The present invention contemplates all individual enantiomers or diastereomers, as well as mixtures of the enantiomers and diastereomers of said compounds including racemates. It is preferred that compounds of Formula I containing at least one chiral center exist as single enantiomers or diastereomers. The single enantiomers or diastereomers may be prepared beginning with chiral reagents or by stereoselective or stereospecific synthetic techniques. Alternatively, the single enantiomers or diastereomers may be isolated from mixtures by standard chiral chromatographic or crystallization techniques.

It will be understood by the skilled reader that most or all of the compounds of the present invention are capable of forming salts. In all cases, the pharmaceutically acceptable salts of all of the compounds are included in the names of them. The compounds of the present invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid.

While all of the compounds of Formula I are useful inhibitors of GSK-3, certain classes of compounds are preferred. The following paragraphs describe such preferred classes:

aa) W-X-Y is -CH₂-CH₂-CH₂-;

ab) W-X-Y is -CH(R^{3'})-N(R²)-CH(R³)-;

ac) R is -(CH₂)_n-;

ad) m is 0, 1, or 2;

- ae) m is 0;
af) n is 0, 1, 2, or 3;
ag) n is 1;
ah) n is 3;
5 ai) R^1 is H;
aj) R^2 is H;
ak) R^2 is $-\text{CO}_2R^7$;
al) R^7 is $\text{C}_1\text{-C}_6$ alkyl;
am) R^7 is tert-butyl;
10 an) R^2 is $(\text{C}_1\text{-C}_4 \text{ alkylene})\text{-R}^5$;
ao) R^2 is methyl;
ap) R^2 is $-\text{C}(\text{O})\text{R}^6$;
aq) R^2 is acetyl;
ar) R^2 is propanoyl;
15 as) R^2 is $-\text{C}(\text{O})(\text{NR}^8\text{R}^9)$;
at) R^2 is $-\text{CONH}_2$;
au) R^2 is $-\text{CONHCH}_3$;
av) R^2 is $-\text{CON}(\text{CH}_3)_2$;
aw) R^2 is $-\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$;
20 ax) R^2 is $-\text{SO}_2\text{CH}_3$;
ay) R^3 is H and $R^{3'}$ is $\text{C}_1\text{-C}_4$ alkyl;
az) R^3 is $\text{C}_1\text{-C}_4$ alkyl and $R^{3'}$ is H;
ba) R^3 and $R^{3'}$ are both H;
bb) R^3 is methyl;
25 bc) $R^{3'}$ is methyl;
bd) Ar is benzofur-4-yl;
be) Ar is benzofur-7-yl;
bf) Ar is 2,3-dihydrobenzofur-4-yl;
bg) Ar is 1-(R^{11})indol-4-yl;
30 bh) Ar is 1-(R^{11})benzimidazol-4-yl;
bi) Ar is imidazo[1,2-a]pyridin-3-yl;
bj) Ar is imidazo[1,2-a]pyridin-7-yl;

bk) Ar is furo[3,2-c]pyridin-3-yl;

bl) R¹¹ is hydrogen;

bm) R¹¹ is $-(CH_2)_p-G$;

bn) p is 3;

5 bo) G is hydroxy;

bp) R¹² is halo;

bq) R¹² is fluoro;

br) R¹² is hydroxy;

bs) R¹² is C₁-C₄ alkoxy;

10 bt) R¹² is methoxy;

bu) R¹² is $-NHC(O)(C_1-C_4 \text{ alkyl})$;

bv) R¹² is $-NHC(O)CH_3$;

bw) R¹³ is fluoro;

bx) The compound is a free base;

15 by) The compound is a salt;

bz) The compound is the hydrochloride salt.

It will be understood that the above classes may be combined to form additional preferred classes.

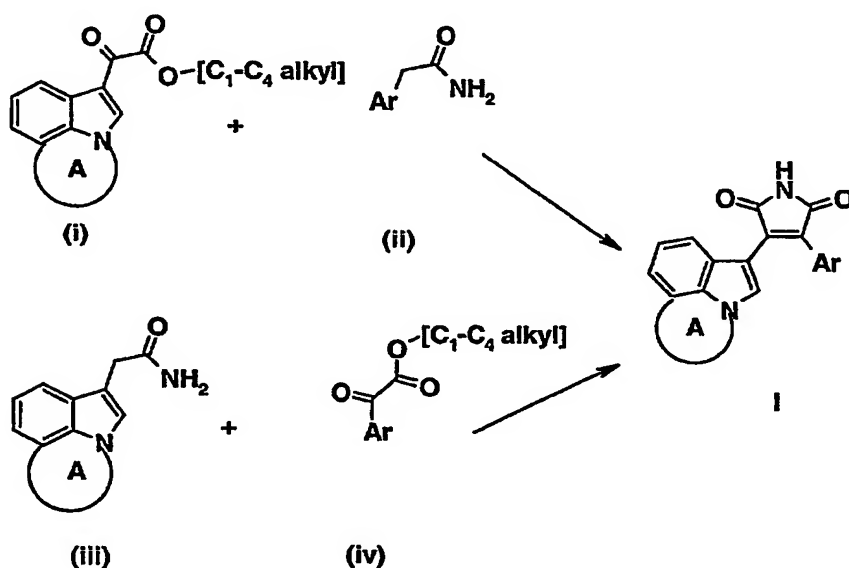
20 The compounds of Formula I are inhibitors of GSK-3. Thus, the present invention also provides a method of inhibiting GSK-3 in a mammal that comprises administering to a mammal in need of said treatment a GSK-3 inhibiting amount of a compound of Formula I. The present compounds are believed to be useful in treating Type I and/or Type II diabetes. Furthermore, the compounds of the present invention are believed to be useful in the treatment of neurological disorders such as dementias, especially dementia of 25 the Alzheimer's type. The compounds of the present invention are also believed to be useful for the treatment of bipolar disorder. It is preferred that the mammal to be treated by the administration of the compounds of Formula I is human.

30 The compounds of the present invention can be prepared by a variety of procedures, some of which are illustrated in the Schemes below. It will be recognized by one of skill in the art that the individual steps in the following schemes may be varied to provide the compounds of Formula I. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being

synthesized, the starting compound, and the relative lability of the substituted moieties. Some substituents have been eliminated in the following schemes for the sake of clarity and are not intended to limit the teaching of the schemes in any way.

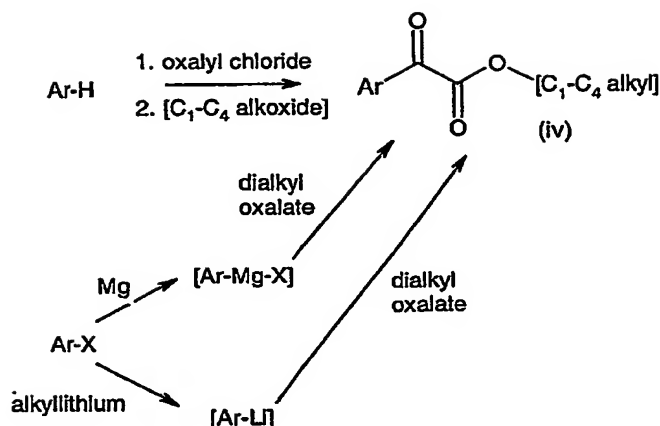
- 5 The compounds of Formula I are prepared from an appropriately substituted oxoacetic acid ester and an appropriately substituted acetamide as illustrated in Scheme I essentially as described by Faul, *et al.*, *J. Org. Chem.* **63**, 6053-6058 (1998), where the ring designated "A" corresponds to the annulated rings of Formula I.

Scheme I



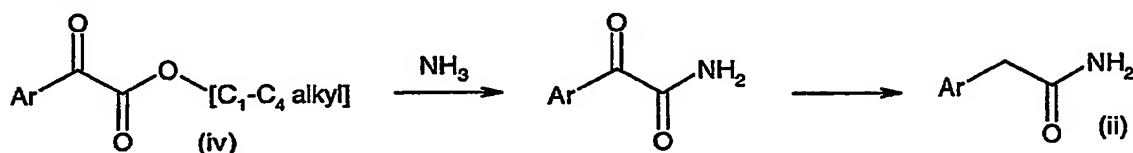
- 10 The oxoacetic acid esters of formula (i) or (iv) are reacted with an acetamide of formula (ii) or (iii), respectively, in a suitable solvent, such as tetrahydrofuran, in the presence of a suitable base, preferably potassium *tert*-butoxide. The condensation reaction is conducted at a temperature from about 0°C to about room temperature, and the reactants are stirred for 1-24 hours. The reaction mixture is treated with a suitable acid,
- 15 such as hydrochloric acid, after which the mixture is stirred at about ambient temperature for 1-24 hours. The resulting maleimide may be isolated by standard techniques, and purified by crystallization or chromatography as necessary or desired.

- 20 The requisite oxoacetic acid esters of formulae (iv) are prepared from appropriately substituted Ar groups by methods well known to the skilled artisan as illustrated in Scheme II, where X is bromo or iodo.

Scheme II

An appropriately substituted Ar is reacted with an oxalyl halide, such as oxalyl chloride, in the presence of an organic base, such as 2,6-lutidine or triethylamine, in an appropriate solvent, such as dichloromethane or diethyl ether, to give the corresponding Ar-oxalyl halide. The reaction is performed at from 0°C to reflux for from 1-24 hours. The mixture is cooled to about -78°C and an alkoxide source, such as sodium methoxide, is added in an appropriate solvent, such as methanol. The resulting oxoacetic acid ester may be isolated by standard techniques and purified by crystallization or chromatography as necessary or desired. Alternatively, a compound of Formula Ar-X is subjected to a lithium-halogen exchange, following which the lithium anion is quenched by an appropriate dialkyl oxalate to provide the desired oxoacetic acid ester. Alternatively, the subject oxoacetic acid esters may be prepared by first reacting a compound of Formula Ar-X with magnesium and then quenching the resulting Grignard reagent with a dialkyl oxalate under standard conditions.

The requisite acetamides of formula (ii) may be prepared from the corresponding oxoacetic acid ester of formula (iv) as illustrated in Scheme III.

Scheme III

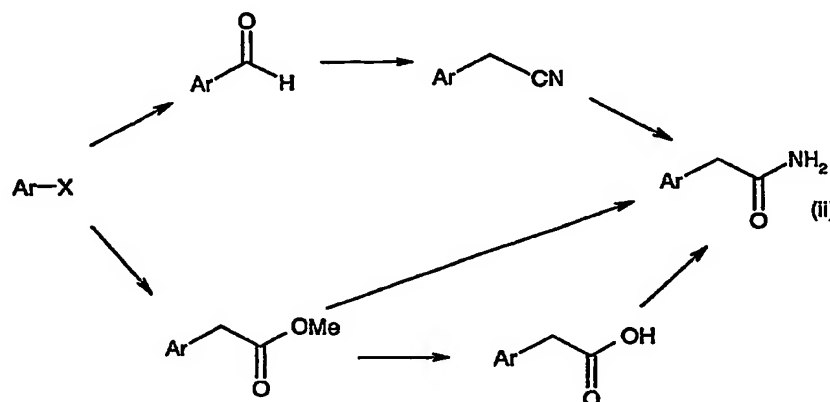
The oxoacetic acid ester (iv) is reacted with ammonia or ammonium hydroxide in a suitable solvent, such as tetrahydrofuran or diethyl ether. The reaction is conducted at

about 0°C for 1-12 hours, after which the reaction mixture is allowed to warm to about ambient temperature. The resulting ketoamide may be isolated by standard techniques and purified by crystallization or chromatography as necessary or desired. This ketoamide is then reduced by reaction with a metal catalyst, such as palladium, and sodium

- 5 hypophosphite in a suitable solvent, such as tetrahydrofuran, dioxane, or dimethylformamide. The reaction is conducted under nitrogen at about reflux conditions for 1-12 hours. The resulting acetamide is isolated by standard techniques and may be purified by crystallization or chromatography as necessary or desired.

10 Alternatively, the requisite acetamides may be prepared from an appropriate Ar-X by standard functional group transformations well known to the skilled artisan as illustrated in Scheme IV (see, Larock, Comprehensive Organic Transformations, 2nd Ed., John Wiley & Sons, New York, pg. 1988-1989 (1999)).

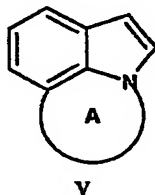
Scheme IV



- 15 The compounds of formula Ar-X may be converted to the corresponding aldehyde by reaction with an appropriate alkyllithium under standard conditions, and the quenching with N,N'-dimethylformamide. This aldehyde is then converted to the corresponding acetonitrile via a phosphorylated cyanohydrin formed in situ by reaction with diethylcyano-phosphonate and lithium cyanide in a suitable solvent, such as
- 20 tetrahydrofuran. For similar examples of this conversion see, Yoneda, et al., Tetrahedron Lett., **30**, 3681-3684 (1989); Yoneda, et al., J. Org. Chem., **56**, 1827-1832 (1991). Base hydrolysis of the acetonitrile provides the desired acetamides (ii). Alternatively, Ar-X may be reacted with 2-ethoxy-2-oxoethylzinc bromide with a palladium catalyst in a suitable solvent, such as tetrahydrofuran, to provide the corresponding arylacetic acid

ester. This ester may be reacted with ammonia directly in a sealed tube with a suitable solvent at elevated temperature to provide the requisite acetamide. Alternatively, the arylacetic acid ester is subjected to base hydrolysis to provide the corresponding aryl acetic acid, and this acid subjected to standard peptide coupling conditions in the presence of a source of ammonia, such as ammonium hydroxide or ammonia gas. Suitable coupling reagents include N,N'-carbonyldiimidazole (CDI), N,N'-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (EDC), and 1-(3-(1-pyrrolidinyl)propyl)-3-ethylcarbodiimide (PEPC). Suitable optional catalysts for the coupling reaction include N,N-[dimethyl]-4-aminopyridine (DMAP). All of the reagents are combined in a suitable solvent, typically dichloromethane, chloroform, tetrahydrofuran, dioxane, or diethyl ether, and are stirred for from 1 to 72 hours at a temperature of from ambient to about the reflux temperature of the solvent. The desired product may be isolated by standard extractive and crystallization techniques, and purified by chromatography or crystallization as necessary or desired.

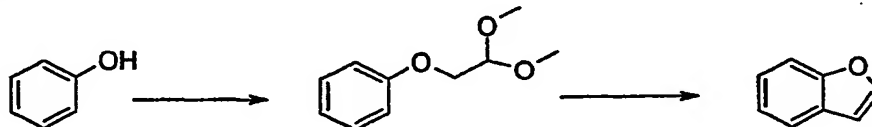
The annulated-indole oxoacetic acid esters (i) and annulated-indole acetamides (iii) may be similarly prepared from the corresponding annulated-indoles of formula (v):



where the ring designated "A" corresponds to the annulated ring in Formula I.

The requisite aryl intermediates for the formation of formula (ii) or (iv) are either commercially available or may be prepared by methods well known to the skilled artisan. The requisite benzofurans, for example, may be prepared as described in Scheme V.

Scheme V

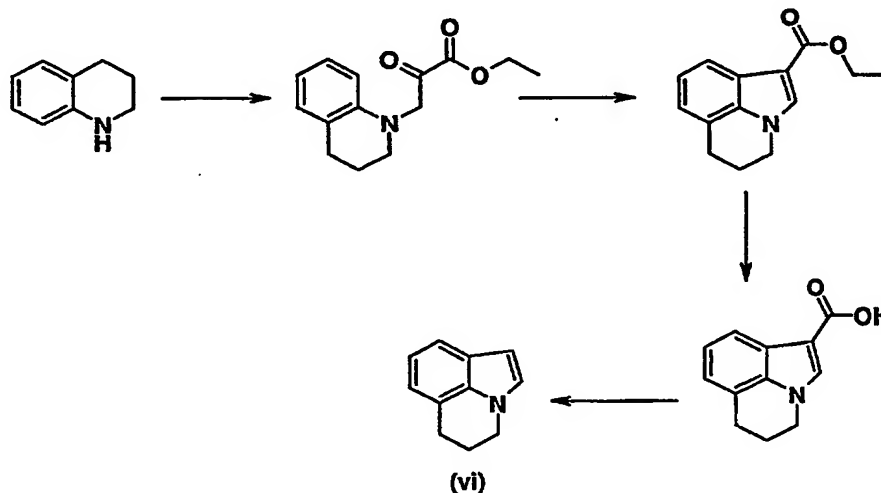


Appropriately substituted phenols are O-alkylated with bromoacetaldehyde dimethyl or diethyl acetal and a suitable base, such as potassium carbonate. Cyclization is accomplished in a suitable solvent, such as chlorobenzene at refluxing temperatures.

The requisite indoles are either commercially available or may be prepared by methods well known in the art. Indole syntheses are described in Robinson, *The Fischer Indole Synthesis*, Wiley, New York (1983); Hamel, *et al.*, *Journal of Organic Chemistry*, **59**, 6372 (1994); and Russell, *et al.*, *Organic Preparations and Procedures International*, **17**, 391 (1985).

The requisite annulated-indoles are prepared by a variety of methods depending upon the specific structure of the ring system. Synthetic methodologies leading to the various annulated-indoles are illustrated in the following schemes and discussed in the following paragraphs. The preparations and examples further illustrate these basic routes as well as modifications to these routes to prepare certain requisite substituted variants. Substituents have been removed from the structures in the following schemes for the sake of clarity, and are not intended to limit the scope of the invention in any way.

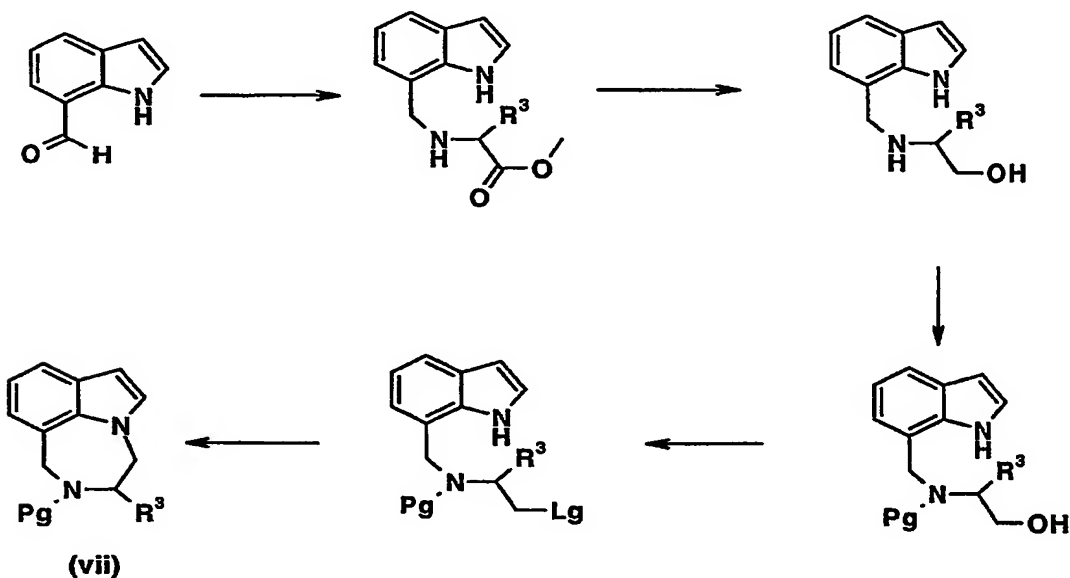
5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolines



An appropriately substituted 1,2,3,4-tetrahydroquinoline is reacted with ethyl bromopyruvate in an appropriate solvent, such as dimethylformamide or tetrahydrofuran. The reaction mixture is stirred for 1-30 hours. The product from this reaction is isolated by standard techniques and is then reacted with an appropriate magnesium halide, typically magnesium chloride, and an appropriate alcohol such as methoxyethanol in an

appropriate cosolvent, such as tetrahydrofuran or dimethylformamide. The skilled artisan will appreciate that the addition must be performed slowly and carefully, after which the resulting reaction mixture is stirred for 1-12 hours at about reflux. The resulting carboxylic acid ester is isolated by standard techniques. This ester is then hydrolyzed and decarboxylated under standard conditions to provide compounds of formula (vi).

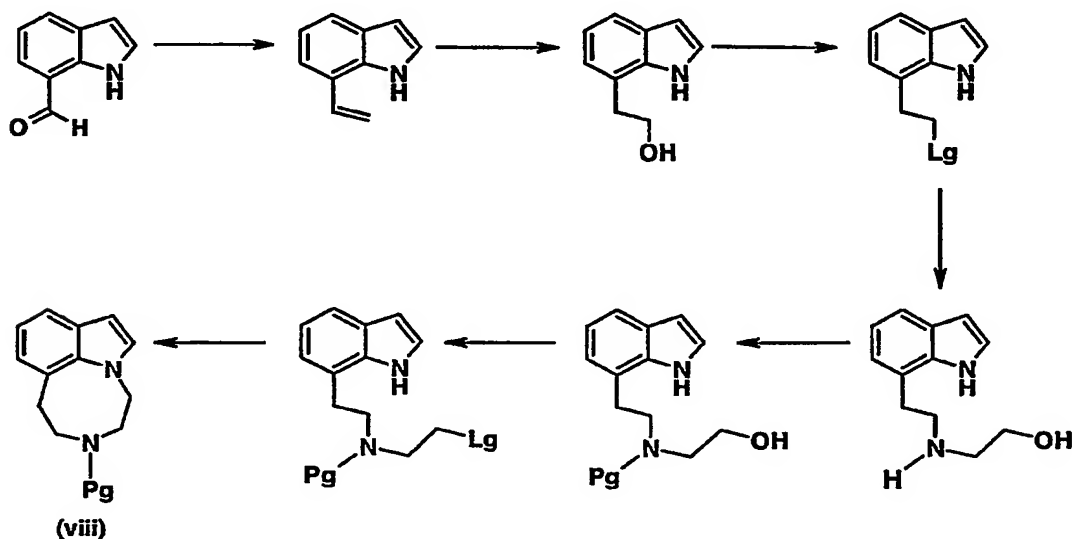
6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indoles



An appropriately substituted indole-7-carboxaldehyde in an appropriate solvent, such as 1,2-dichloroethane, is reacted with an appropriately substituted amino acid methyl ester and acetic acid. This reaction is conducted under nitrogen at about ambient temperature in the presence of a mild reducing agent, such as sodium cyanoborohydride or sodium triacetoxyborohydride. The reaction mixture is stirred for about 24 hours, and the resulting amino ester is isolated by standard techniques. The ester moiety is reduced to the corresponding alcohol by treatment with a suitable reducing agent, typically lithium aluminum hydride, in an appropriate solvent, typically tetrahydrofuran or diethyl ether. The secondary amine moiety is now reacted with an appropriate reagent to introduce a suitable amino protecting group "Pg", such as a formyl group, acetyl group, or preferably a *tert*-butoxycarbonyl moiety. Techniques for the introduction of these groups are well known to the skilled artisan. A solution of this compound in an appropriate solvent, such as dichloromethane or diethyl ether, is reacted with an appropriate reagent to activate the

hydroxy moiety, providing a leaving group ("Lg"). The skilled artisan will appreciate that appropriate leaving groups include halides, oxonium ions, alkyl perchlorates, ammonio-alkanesulfonate esters, alkyl fluorosulfonates, nonaflates, tresylates, triflates, and sulfonic esters, preferably the mesylate or tosylate. Techniques for the introduction of these groups are well known to the skilled artisan. (See for example: March, "Advanced Organic Chemistry," John Wiley and Sons, New York, N.Y., 1992, pg. 352-362). The activated compound is then dissolved in an appropriate solvent, such as tetrahydrofuran, diethyl ether or N,N-dimethylformamide and is reacted with a strong base, such as potassium hydride or sodium hydride. The reaction is conducted under nitrogen at about 0°C and stirred for 30-120 minutes. The compound of formula (vii) is isolated and purified by standard techniques. The skilled artisan will appreciate that the nitrogen-protecting groups may be removed at any convenient point in the synthesis of the compounds of the present invention. Methods of removing an amino-protecting group are well known in the art (for example, see: T.W. Greene, "Protective Groups in Organic Synthesis," John Wiley and Sons, New York, N.Y., 1991, Chapter 7).

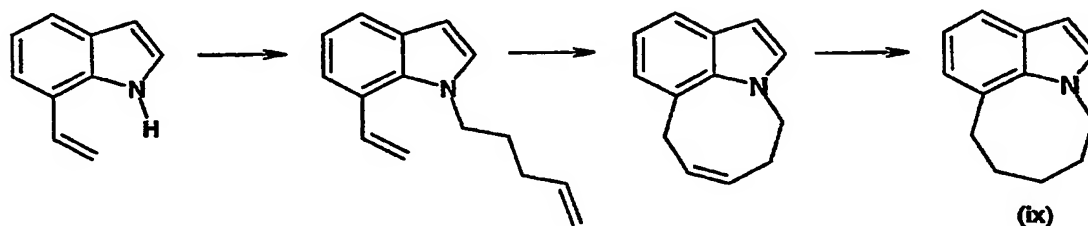
5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indoles



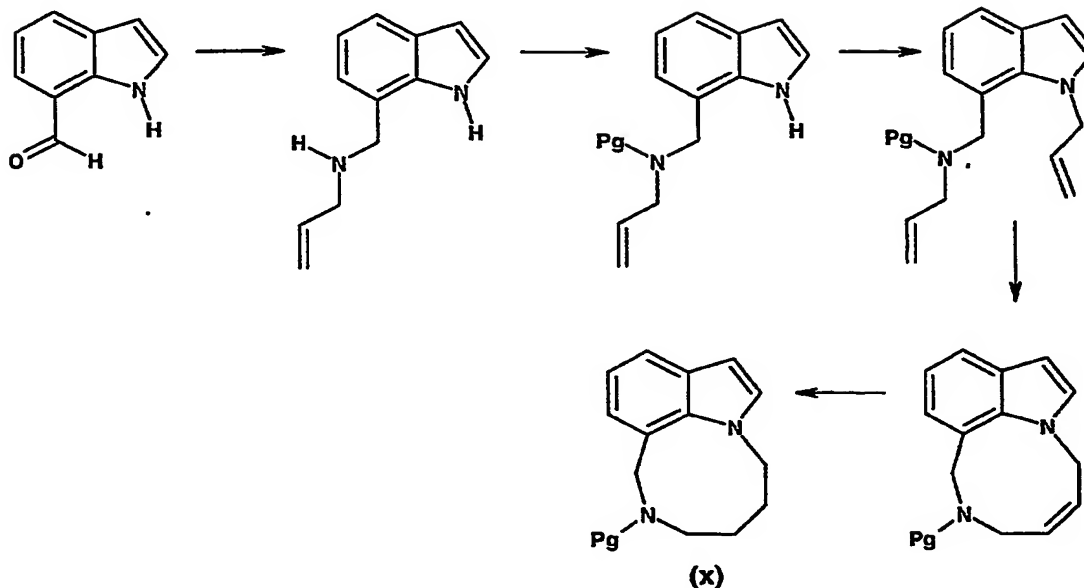
An appropriately substituted indole-7-carboxaldehyde in an appropriate solvent, such as tetrahydrofuran or toluene, is reacted with a suitable methylenating reagent at about ambient temperature. Suitable methylenating reagents include Tebbe reagent (μ -

chloro- μ -methylene[bis(cyclopentadienyl)titanium]dimethylaluminum) and appropriate Wittig reagents, such as methyltriphenylphosphonium bromide, in the presence as a suitable base, such as potassium *tert*-butoxide. The reaction mixture is stirred for 1-6 hours, after which the resultant vinylindole is isolated under standard techniques. This compound is then hydroborated and oxidized under standard conditions to provide the corresponding hydroxyethylindole. This alcohol is then activated as previously described, and reacted with ethanolamine or an appropriate amino acid ester. When aminoethanol is employed, the resulting alcohol is activated and the compound cyclized as previously described. When an amino acid ester is employed, the resulting ester is first reduced, and then activated and the compound cyclized as previously described to provide compounds of formula (xiii). The skilled artisan will appreciate that the nitrogen-protecting groups may be removed at any convenient point in the synthesis of the compounds of the present invention.

15 Pyrrolo[3,2,1-kl]benzo[b]azacyclooctane



An appropriately substituted 7-vinylindole is alkylated with an appropriate bromoalkene under standard conditions and the resulting diene is reacted with bis(tricyclohexyl-phosphine)benzylidene ruthenium (IV) dichloride (Grubb's catalyst) at room temperature in a suitable solvent, such as dichloromethane. After about 24 hours the cyclized alkene is isolated by standard techniques. The double bond may then be reduced under standard hydrogenation conditions to provide the compounds of formula (ix).

[1,5]diazaperhydroonino[8,9,1-hi]indoles

An appropriately substituted indole-7-carboxaldehyde is reductively aminated with
 5 allylamine in the presence of a suitable acid, such as acetic acid, and an appropriate
 reducing agent, such as sodium cyanoborohydride or sodium triacetoxyborohydride in an
 appropriate solvent, such as 1,2-dichloroethane. The mixture is stirred at room
 temperature for about 24 hours and the resulting amine is isolated and purified by
 standard techniques. The amine is then protected as previously described and the indole
 10 nitrogen alkylated with allyl bromide under standard conditions. The diene is then
 cyclized as previously described to provide the cyclic alkene. The double bond may then
 be reduced under standard hydrogenation conditions to provide the compounds of formula
 (x). The double bond may also be oxidized to introduce the diol functionality.

The skilled artisan will appreciate that the general synthetic schemes discussed in
 15 the preceding paragraphs may be modified by methods well known in the art to provide
 the remaining annulated indoles necessary to prepare the compounds of the present
 invention.

Many of the compounds of the present invention are not only inhibitors of GSK-3,
 but are also useful intermediates for the preparation of additional compounds of the
 20 present invention. For example, secondary amines may be acylated, alkylated or coupled
 with carboxylic acids or amino acids under standard peptide coupling conditions.

Furthermore, ester moieties may be reduced to the corresponding alcohols or converted to amides under standard conditions. Alcohols may be activated and displaced by a number of nucleophiles to provide other compounds of the invention. Such leaving groups include but are not limited to halides, oxonium ions, alkyl perchlorates, ammonioalkanesulfonate esters, alkyl fluorosulfonates, nonaflates, tresylates, triflates, and sulfonic esters, preferably the mesylate or tosylate. Techniques for the introduction of these groups are also well known to the skilled artisan; see, for example, March, Advanced Organic Chemistry, 5th Ed., John Wiley and Sons, New York, pg. 445-449 (2001).

10 The skilled artisan will also appreciate that not all of the substituents in the compounds of Formula I will tolerate certain reaction conditions employed to synthesize the compounds. These moieties may be introduced at a convenient point in the synthesis, or may be protected and then deprotected as necessary or desired. The skilled artisan will appreciate that the protecting groups may be removed at any convenient point in the
15 synthesis of the compounds of the present invention. Methods for introducing and removing nitrogen and oxygen protecting groups are well known in the art; see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons, New York, Chapter 7 (1999). Furthermore, the skilled artisan will appreciate that in many circumstances, the order in which moieties are introduced is not critical. The
20 particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties.

Preparation 1

25 5-fluoro-1,2,3,4-tetrahydroquinoline

5-fluoroquinoline

Add sodium nitrite in portions to a suspension of 5-aminoquinoline (50 g, 347 mmol) in 48% HBF₄ (200 mL) at 0°C. Stir for 1 hour and then pour into 1:1 diethyl ether/ ethyl acetate (500 mL). Filter the resulting suspension and dry the solid. Add
30 this solid (82.5 g, 338 mmol) in portions to refluxing xylene (1 L), stir for 2 hours, and then cool. Decant the xylene and dissolve the residue in 1N hydrochloric acid (600 mL). Neutralize with sodium carbonate, extract with ethyl acetate (10 x 500

mL), dry the extracts over sodium sulfate, filter and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 10-20% diethyl ether in hexanes. Combine fractions containing product and concentrate them under reduced pressure to provide the desired compound (28.1 g, 55%).

5 MS (EI, m/z) C_9H_6FN (M+1) 148.0

Reduction

10 Shake a mixture of 5-fluoroquinoline (28.1 g) and 5% palladium on carbon (5.6 g) in methanol over night at 40°C under 60 psi hydrogen. Filter the mixture through Celite and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 5-10% ethyl acetate in hexanes. Combine fractions containing product and concentrate them under reduced pressure to provide the title compound (22.5 g, 78%).

15 MS (EI, m/z) $C_9H_{10}FN$ (M+1) 152.0

Preparation 2

6-Fluoro-1,2,3,4-tetrahydroquinoline

Beginning with 6-aminoquinoline, the title compound is prepared essentially as described in Preparation 1.

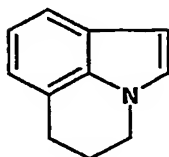
20 MS (EI, m/z) $C_9H_{10}FN$ (M+1) 152.0.

Preparation 3

5-Chloro-1,2,3,4-tetrahydroquinoline

25 A mixture of 5-chloroquinoline (10.0 g) and platinum oxide (50 mg) in acetic acid was shaken under a hydrogen atmosphere at room temperature for 4 hours. The mixture was diluted with diethyl ether and filtered through Celite. The volatiles were removed under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate (3 x 300 mL). The organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The
30 residue was purified over silica gel and the fractions containing product were combined and concentrated under reduced pressure to provide 7.0 g (69%) of the desired compound.

Preparation 4



5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinoline

3-(3,4-Dihydro-2H-quinolin-1-yl)-2-oxopropionic acid ethyl ester

- 5 Add bromoethyl pyruvate (40 mL, 0.29 mol) to a solution of 1,2,3,4-tetrahydroquinoline (75.5 mL, 0.59 mol) in tetrahydrofuran (300 mL) dropwise over 30 minutes. Stir for 24 hours, filter the reaction mixture, rinse the filter cake well with tetrahydrofuran (100 mL), and concentrate the filtrate under reduced pressure to provide the desired compound as a red oil (79.7 g).

10

5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carboxylic acid ethyl ester

- Add magnesium chloride (27.7 g, 0.29 mol) to 2-methoxyethanol (400 mL) and heat the mixture to reflux. Add a solution of 3-(3,4-Dihydro-2H-quinolin-1-yl)-2-oxopropionic acid ethyl ester (0.29 mol) in 2-methoxyethanol (100 mL) and tetrahydrofuran (40 mL) slowly to the MgCl_2 mixture over 1 hour. Upon completion of addition, stir the mixture for 5 hours at reflux, and then concentrate under reduced pressure. Treat the concentrated crude mixture with 2N hydrochloric acid (500 mL) and extract with dichloromethane (3 x 400 mL). Combine the organic layers, dry over sodium sulfate, filter, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 20% ethyl acetate/hexanes. Combine fractions containing product and concentrate them under reduced pressure to provide the desired compound as an orange solid (31.6 g, 48%).

15

20

MS (IS, m/z) $\text{C}_{14}\text{H}_{15}\text{NO}_2$ ($\text{M}^+ + 1$) = 230.

- 25 5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carboxylic acid

Add 5 N aqueous sodium hydroxide (60 mL, 0.3 mol) to a solution of 5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carboxylic acid ethyl ester (31 g, 0.14 mol) in ethanol (200 mL) and water (70 mL) and stir the resulting mixture at reflux for 3 hours. Cool the reaction mixture to 20-24°C, dilute with water (2 L), and wash sequentially with

dichloromethane (2 x 200 mL) and diethyl ether (1 x 200 mL). Filter the aqueous layer through Celite and treat the filtrate with concentrated hydrochloric acid (25 mL) to precipitate the product. Filter the solid, wash with water (200 mL), and dry under reduced pressure to give the desired compound as a light yellow solid (23.2 g, 85%).

5 MS (IS, m/z) $C_{12}H_{11}NO_2$ ($M^+ + 1$) = 202.

Decarboxylation

Add copper chromite (1.5 g, 4.8 mmol) to a solution of 5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carboxylic acid (3.7 g, 18.4 mmol) in 20 mL of quinoline.

10 Stir the resulting mixture at 185°C for 4 hours and then cool to 20-24°C, dilute with dichloromethane (100 mL), and filter through Celite. Wash the filtrate sequentially with 2 N hydrochloric acid (2 x 50 mL) and 2 N aqueous sodium hydroxide (25 mL).

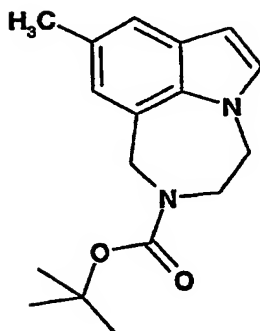
Concentrate the remaining organic phase under reduced pressure and then subject the residue to silica gel chromatography, eluting with 5% EtOAc/Hexanes. Combine
15 fractions containing product and concentrate them under reduced pressure to provide the title compound as a light tan solid (1.67 g, 58%).

1H -NMR(400 MHz, DMSO- d_6): δ 7.31-7.29 (d, 1 H, J = 7.8 Hz), 7.28-7.27 (d, 1 H, J = 2.93 Hz), 6.9-6.86 (t, 1 H, J = 7.6 Hz), 6.82-6.8 (dd, 1 H, J = 6.8, 1.0 Hz), 6.33-6.32 (d, 1 H, J = 2.93 Hz), 4.15-4.12 (t, 2 H, J = 5.6 Hz), 2.92-2.89 (t, 2 H, J = 6.1 Hz), 2.15-2.08
20 (m, 2 H).

The compounds of Preparations 5 – 8 are prepared essentially as described in Preparation 4.

Prep.	Compound	Data (m/z)
5	7-fluoro-5,6-dihydro-4H-pyrrolo[3,2,1-j]quinoline	MS(EI): 176.1(M+1)
6	8-fluoro-5,6-dihydro-4H-pyrrolo[3,2,1-j]quinoline	MS(EI): 175.1(M ⁺)
7	7-chloro-5,6-dihydro-4H-pyrrolo[3,2,1-j]quinoline	MS(EI): 192.1(M ⁺)
8	8-chloro-5,6-dihydro-4H-pyrrolo[3,2,1-j]quinoline	MS(IS): 191.9(M ⁺)

Preparation 9



9-methyl-6-(~~tert~~-butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indole
5-Methyl-1*H*-indole-7-carbaldehyde

5 Dissolve 5-methyl-2-nitrobenzaldehyde (7.84 g, 47.52 mmol), 1-butanol (10.55 g, 142.6 mmol) and 4-toluenesulfonic acid monohydrate (0.5 g, 2.6 mmol) in toluene (200 mL). Heat the reaction mixture to reflux with constant water removal (Dean-Stark Trap). Continue to heat the reaction mixture for 3 hours. Add water and extract the aqueous layer with ethyl acetate. Combine the organic layers and dry over sodium sulfate, filter, 10 concentrate under reduced pressure, and purify by flash chromatography (1% v/v triethylamine buffered silica gel, 5% ethyl acetate/hexane) to give the dibutyl acetal derivative as a colorless oil (14 g, 99%).

Dissolve 2-Dibutoxymethyl-4-methyl-1-nitrobenzene (13.957 g, 47.373 mmol) in anhydrous tetrahydrofuran (474 mL) under nitrogen, and cool the solution to -40°C . Add 15 vinylmagnesium bromide (190 mL, 190 mmol, 1.0 M in tetrahydrofuran) at -40°C with stirring. Stir the reaction mixture for 40 minutes and add saturated aqueous ammonium chloride. Extract the aqueous layer with ethyl acetate. Combine the organic layers, dry over sodium sulfate, filter, and concentrate. Dissolve the residue in tetrahydrofuran (160 mL) and cool to 0°C . Add aqueous 0.5 molar hydrochloric acid (20 mL) and stir the 20 mixture at 0°C for 1 hour. Add saturated aqueous sodium hydrogen carbonate (200 mL) and extract the aqueous layer with ethyl acetate (3×200 mL). Combine the organic layers, dry over anhydrous sodium sulfate, filter, concentrate under reduced pressure and purify by flash column chromatography (silica gel, 5% ethyl acetate/hexane) to give the title compound as a white solid.

¹H-NMR(CDCl₃): δ 10.10 (s, 1H), 10.06 (s, 1H), 7.72 (s, 1H), 7.40 (s, 1H), 7.28 (m, 1H), 6.54 (m, 1H), 2.50 (s, 3H).

N-[2-hydroxyeth-1-yl] (5-Methyl-1*H*-indol-7-yl)methylamine

5 Dissolve 5-Methyl-1*H*-indole-7-carbaldehyde (4.036 g, 25.384 mmol) in absolute methanol (200 mL), add 2-aminoethanol (3.1 g, 50.767 mmol) and 10% palladium on carbon (0.4 g). Stir the mixture for 1 hour under nitrogen, then under 1 atmosphere of hydrogen for 3 hours. Filter, concentrate under reduced pressure, and purify by flash column chromatography (silica gel, 90/9/1, dichloromethane/methanol/ammonia) to give
10 the title compound as a colorless oil.
MS (ES, *m/z*): = 203 (M-1)

N-[tert-butoxycarbonyl] N-[2-hydroxyeth-1-yl] (5-Methyl-1*H*-indol-7-yl)methylamine

Dissolve N-[2-hydroxyeth-1-yl] (5-Methyl-1*H*-indol-7-yl)methylamine (3.0 g,
15 14.706 mmol) in tetrahydrofuran (120 mL) and cool the solution to 0 °C. Add aqueous potassium carbonate (30 mL, 29.41 mmol, 0.98 M solution) and di-tert-butyl dicarbonate (3.53 g, 16.18 mmol). Stir the reaction mixture for 4 hours at 0 °C, add water and extract the aqueous layer with ethyl acetate. Combine the organic layers, dry with anhydrous sodium sulfate, filter, concentrate under reduced pressure and purify by flash column
20 chromatography (silica gel, 20% ethyl acetate/hexane) to give the title compound as a white solid (4.12 g, 92%).
MS(ES, *m/z*): (M-1) = 303.

N-[tert-butoxycarbonyl] N-[2-(methanesulfonyloxy)eth-1-yl] (5-Methyl-1*H*-indol-7-yl)methylamine

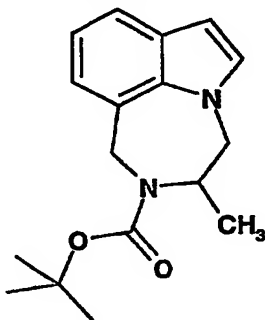
25 Dissolve N-[tert-butoxycarbonyl] N-[2-hydroxyeth-1-yl] (5-Methyl-1*H*-indol-7-yl)methylamine (1.15 g, 3.78 mmol) in tetrahydrofuran (22 mL) under nitrogen and cool to 0°C. Add triethylamine (1.91 g, 18.88 mmol) and methanesulfonic anhydride (0.72 g, 4.15 mmol). Stir the reaction mixture for 2 hours at 0 °C. Add water to the reaction
30 mixture and extract the aqueous layer with ethyl acetate. Combine the organic layers, dry with anhydrous sodium sulfate, filter, and concentrate under reduced pressure to give the desired compound as colorless oil.

$^1\text{H-NMR}(\text{CDCl}_3)$: δ 9.93 (s, 1H), 7.40 (s, 1H), 7.19 (t, 1H), 6.86 (s, 1H), 6.45 (t, 1H), 4.67 (s, 2H), 4.13 (t, 2H), 3.53 (t, 2H), 2.72 (s, 3H), 2.44 (s, 3H, CH_3Ar), 1.51 (s, 9H, 3CH_3).

5 Ring Closure

Dissolve N-[tert-butoxycarbonyl] N-[2-(methanesulfonyloxy)eth-1-yl] (5-Methyl-1H-indol-7-yl)methylamine (1.22 g, 3.19 mmol) in anhydrous dimethylformamide (32 mL) under nitrogen and cool to 0 °C. Add sodium hydride (0.15 g, 3.83 mmol, 60% in oil) and stir the reaction mixture for 1 hour at 0°C. Add water and extract the aqueous layer with ethyl acetate. Combine the organic layers, dry with anhydrous sodium sulfate, filter, concentrate under reduced pressure and purify by flash column chromatography (silica gel, 10% ethyl acetate/hexane) to give the title compound as white solid. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.31 (m, 1H), 7.01 (m, 1H), 6.90 and 6.80 (2 singlets, 1H), 6.45 (d, 1H), 4.85 and 4.78 (2 singlets, 2H), 4.22 (m, 2H), 3.93 (m, 2H), 2.43 and 2.41 (2 singlets, 3H, CH_3Ar), 1.45 and 1.44 (2 singlets, 9H, 3CH_3).

Preparation 10



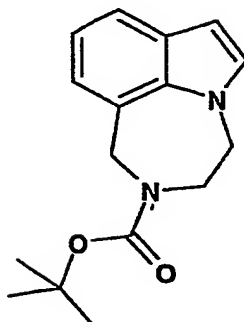
6-(tert-butoxycarbonyl)-5-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indole

Beginning with indole-7-carboxaldehyde and DL-alanine methyl ester hydrochloride (0.72 g, 5.16 mmol), the title compound is prepared essentially as described in Preparation 9.

MS (ES, m/z) ($M + 1$) = 287.0.

-24-

Preparation 11



6-(tert-butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indole

Beginning with indole-7-carboxaldehyde and ethanolamine, the title compound is prepared essentially as described in Preparation 9.

MS(IS, m/z) $C_{16}H_{20}N_2O_2$ ($M^+ + 1$) = 273

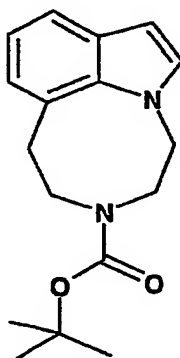
Preparation 12

9-fluoro-6-(tert-butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indole

Beginning with 5-fluoroindole-7-carboxaldehyde and ethanolamine, the title compound is prepared essentially as described in Preparation 9.

MS: (ES, m/z) 291 ($M + 1$).

Preparation 13



6-(tert-butoxycarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indole

7-vinylindole

Add potassium tert-butoxide (1 M in tetrahydrofuran, 14.1 mL, 14.1 mmol) to a solution of methyl triphenylphosphonium bromide (5.05 g, 14.1 mmol) in tetrahydrofuran

(80 mL) and stir the reaction mixture for 45 minutes at room temperature. Add a solution of 7-formylindole (1.00 g, 6.89 mmol) in tetrahydrofuran (10 mL) and stirred for 1.5 hours. Dilute the reaction mixture with ethyl acetate (250 mL), wash sequentially with an 8:1 mixture of water and 1 N hydrochloric acid (2 x 100 mL) and saturated aqueous sodium chloride (100 mL), dry over sodium sulfate, filter, and concentrate the filtrate under reduced pressure. Subject the residue silica gel chromatography. Combine fractions containing product and concentrate them under reduced pressure to provide the desired compound as a brown oil.

MS (IS, m/z) $C_{10}H_9N$ ($M^+ + 1$) = 144

Hydroboration/Oxidation

Add 1 M borane-tetrahydrofuran complex in tetrahydro-furan (9.95 mL, 9.95 mmol) to a 0 °C solution of 7-vinyl-indole (0.95 g, 6.6 mmol) in anhydrous tetrahydrofuran (60 mL) and stir the reaction mixture overnight at room temperature. Add 1 N sodium hydroxide (25 mL) and 30% hydrogen peroxide (35 mL) and stir the mixture at reflux for 1 hour. Cool the reaction mixture to room temperature, dilute with ethyl acetate (100 mL), wash sequentially with water (50 mL) and saturated aqueous sodium chloride (2 x 50 mL), dry over sodium sulfate, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 50% ethyl acetate in hexanes. Combine fractions containing product concentrate them under reduced pressure to provide the desired compound as a yellow oil (0.60 g, 56%).

MS (IS, m/z) $C_{10}H_{11}NO$ ($M^+ + 1$) = 162.

Alcohol Activation

Add a solution of methanesulfonyl chloride (0.29 mL, 3.68 mmol) in dichloromethane (5 mL) dropwise over 30 minutes to a solution of 7-(2-hydroxyethyl)indole (0.54 g, 3.34 mmol) and triethylamine (2.3 mL, 16.7 mmol) in dichloromethane (45 mL). Stir the mixture for an additional 2 hours at room temperature. Dilute the reaction mixture with dichloromethane (50 mL), wash sequentially with water (30 mL) and saturated aqueous sodium chloride (2 x 30 mL), dry over sodium sulfate, filter, and concentrate under reduced pressure.

Nucleophilic Displacement

Add ethanolamine (5 mL, 82 mmol) to a solution of 7-(2-(methanesulfonyloxy)eth-1-yl)indole (0.79 g, 3.3 mmol) in ethanol (50 mL) and stir the reaction mixture at reflux overnight. Dilute with ethyl acetate (150 mL), wash sequentially with water (3 x 50 mL) and saturated aqueous sodium chloride (2 x 50 mL), dry over sodium sulfate, filter, and concentrate under reduced pressure to provide 7-(2-(N-[2-hydroxyeth-1-yl]amino)eth-1-yl)indole as a light-brown solid (0.57 g, 85%).

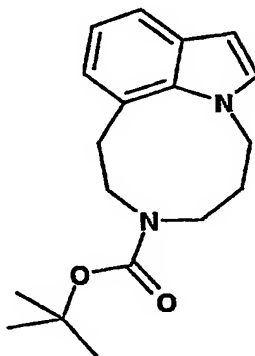
MS (IS, m/z) $C_{12}H_{16}N_2O$ ($M^+ + 1$) = 205

Ring Formation

Beginning with 7-(2-(N-[2-hydroxyeth-1-yl]amino)eth-1-yl)indole, the title compound is prepared essentially as described in Preparation 9.

MS (IS, m/z) $C_{17}H_{22}N_2O_2$ ($M^+ + 1$) = 287

Preparation 14

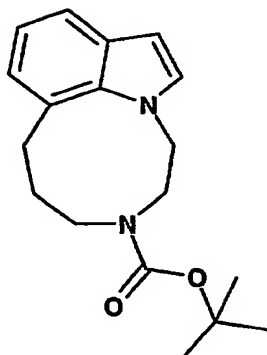
7-(tert-butoxycarbonyl)-[1,6]diazaperhydroonino[8,9,1-hi]indole

Beginning with 7-(2-(N-[3-hydroxyprop-1-yl]amino)eth-1-yl)indole, the title compound is prepared essentially as described in Preparation 9.

MS(ES): m/z = 301.2 ($M^+ + 1$)

-27-

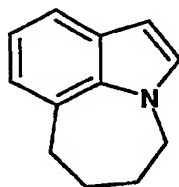
Preparation 15



6-(~~tert~~-butoxycarbonyl)-[1,7]diazaperhydroonino[8,9,1-hi]indole

- Beginning with 7-(3-(N-[2-hydroxyethyl]amino)prop-1-yl)indole, the title
5 compound is prepared essentially as described in Preparation 9.

Preparation 16



4,5,6,7-Tetrahydroazepino[3,2,1-hi]indole

10 3,4-Dihydro-2H-naphthalen-1-one oxime

- Add hydroxylamine hydrochloride (71.0 g, 1.03 mol) to a solution of α -tetralone (100.0 g, 0.68 mol) in 300 mL of methanol and stir the resulting solution at reflux for 2 hours. Cool the mixture to 20-24°C and concentrate under reduced pressure. Dilute the residue with 1 L of water and extract with dichloromethane. Wash the organic layer with
15 saturated aqueous sodium chloride, dry over sodium sulfate, filter, and concentrate under reduced pressure. Crystallize the residue from isopropanol to provide the desired compound as an off-white solid (70.0 g, 63%).

MS (FIA, m/z) $C_{10}H_{11}NO$ ($M^+ + 1$) = 162.4.

1,3,4,5-Tetrahydrobenzo[b]azepin-2-one

Charge a 1L 3-neck round bottom flask equipped with a mechanical stirrer with neat polyphosphoric acid (100 g) and heat the acid heated to 125 °C while stirring under nitrogen. Add 3,4-Dihydro-2H-naphthalen-1-one oxime (15.0 g, 93 mmol) carefully to control exotherm, keeping the temperature below 175 °C. After 10 minutes of heating, cool the mixture 20-24°C and quenched with ice and water. Filter the aqueous suspension and wash the filter cake with water until the filtrate is neutral. Dry the filter cake under vacuum to provide the desired compound as an off-white solid (12.8 g, 85%).

MS (ES, m/z) $C_{10}H_{11}NO$ ($M^+ + 1$) = 161.9

2,3,4,5-Tetrahydro-1H-benzo[b]azepine

Add 80 mL of lithium aluminum hydride (1 M solution in tetrahydrofuran) to a solution of 1,3,4,5-tetrahydrobenzo-[b]azepin-2-one (12.9 g, 80.0 mmol) in 720 mL of tetrahydro-furan. Stir the reaction mixture at reflux for 3 hours and cool to 0 °C. Quench the reaction by the sequential addition of 3 mL of water, 3 mL of 15% sodium hydroxide, and 9 mL of water. Filter the resulting suspension through Celite and rinse the filter cake with ethyl acetate. Concentrate the filtrate under reduced pressure to provide the desired compound as an orange solid (10.0 g, 85%).

MS (FIA, m/z) $C_{10}H_{13}N$ ($M^+ + 1$) = 148.2.

2-Oxo-3-(2,3,4,5-tetrahydrobenzo[b]azepin-1-yl)propionic acid ethyl ester

Add 2,3,4,5-tetrahydro-1H-benzo[b]azepine in small portions to a 0 °C suspension of 60% sodium hydride (3.0 g, 0.12-mol) in 300 mL of dimethylformamide. Upon complete addition of the amine, remove the ice bath and stir the reaction at 20-24°C for 40 minutes. Add ethyl bromopyruvate (22.6 mL, 0.16 mol) and stir the resulting mixture at 20-24°C for 6 hours. Add an additional 5 mL of ethyl bromopyruvate and stir the mixture for 1 hour. Quench by adding 50 mL of water then dilute with 1.5 L of dichloromethane. Separate the layers, wash the organic layer sequentially with water (2 x 500 mL) and saturated aqueous sodium chloride (500 mL), dry over sodium sulfate, filter, and concentrate under reduced pressure at 60 °C. Dissolve the residue in ethyl acetate (500 mL), wash sequentially with water (3 x 100 mL) and saturated aqueous sodium

chloride, dry over sodium sulfate, filter, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 5-10% EtOAc/hexanes to provide the desired compound as an off white solid (7.0 g, 40%).

MS (FID, m/z) $C_{15}H_{19}NO_3$ (M^+) = 261.13.

5

4,5,6,7-Tetrahydroazepino[3,2,1-hi]indole-1-carboxylic acid ethyl ester

Add magnesium chloride (2.55 g, 26.8 mmol) to 30 mL of 2-methoxyethanol and heat the mixture to reflux. Add a solution of 2-oxo-3-(2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)propionic acid ethyl ester (7.0 g, 26.8 mmol) in 2-methoxyethanol (20 mL) over 1 hour. Stir the resulting mixture for 6 hours at reflux, cool to 20-24°C, and concentrate under reduced pressure. Dilute the residue with 400 mL of dichloromethane and wash sequentially with 2 N hydrochloric acid (100 mL), saturated aqueous sodium bicarbonate (100 mL) and saturated aqueous sodium chloride (100 mL), dry over sodium sulfate, filter, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 20% ethyl acetate in hexane. Combine fractions containing product and concentrate them under reduced pressure to provide the desired compound as a yellow oil (3.1 g, 48%).

MS (FIA, m/z) $C_{15}H_{17}NO_2$ ($M^+ + 1$) = 244.4.

20 4,5,6,7-Tetrahydroazepino[3,2,1-hi]indole-1-carboxylic acid

Add powdered sodium hydroxide (0.71 g, 17.8 mmol) to a solution of 4,5,6,7-tetrahydroazepino[3,2,1-hi]indole-1-carboxylic acid ethyl ester (2.0 g, 8.22 mmol) in ethanol (13 mL) and water (9 mL) and stir the resulting mixture at reflux for 4 hours. Cool the reaction mixture to room temperature, dilute with water (100 mL) and wash with dichloromethane (2 x 50 mL). Separate the layers, filter the aqueous layer through Celite and acidify the filtrate with concentrated hydrochloric acid. Filter the suspension, wash the recovered solid with water, and dry under reduced pressure to provide the desired compound as a white solid (1.59 g, 90%).

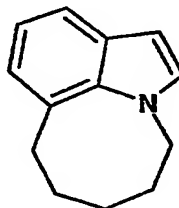
MS (FIA, m/z) $C_{13}H_{13}NO_2$ ($M^+ + 1$) = 216.3

30

Decarboxylation

- Add copper chromite (0.55 g, 1.77 mmol) to a solution of 4,5,6,7-tetrahydroazepino[3,2,1-hi]indole-1-carboxylic acid (1.4 g, 6.5 mmol) in 7.5 mL of quinoline and stir the resulting mixture at 185°C for 4 hours. Cool the reaction mixture to room temperature, dilute with dichloromethane and filter through Celite. Wash the filtrate sequentially with 2 N hydrochloric acid (2 x 25 mL) and 2 N sodium hydroxide (25 mL). Concentrate the organic layer under reduced pressure and subject the residue to silica gel chromatography, eluting with 5% EtOAc/Hexane to provide the title compound as an orange solid (0.85 g, 76%).
- MS (EI, m/z) $C_{12}H_{13}N$ (M^+) = 171.4

Preparation 17



Pyrrolo[3,2,1-kl]benzo[b]azacyclooctane

15 7-Vinyl-1H-indole

- Add tributyl(vinyl)tin (9.8 mL, 33.7 mmol), triphenyl-phosphine (0.4 g, 1.53 mmol), diphenylpalladium(II) dichloride (1.07 g, 1.53 mmol) and lithium chloride (4.0 g, 94.4 mmol) to 7-bromo-1H-indole (6.0 g, 30.6 mmol) in 150 mL of dimethylformamide and heat the resulting mixture at 100°C overnight. Cool the reaction mixture to 20-24°C and poured into a mixture of 150 mL of water and 150 mL of ethyl acetate. Wash the aqueous layer with additional ethyl acetate (3 x 100 mL), combine the organic layers, wash with saturated aqueous sodium chloride, dry over magnesium sulfate, filter, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 5-10% ethyl acetate in hexanes. Combine fractions containing product and concentrate them under reduced pressure to provide the desired compound as a clear oil (3.5 g, 80%).
- MS (FIA, m/z) $C_{10}H_9N$ ($M^+ + 1$) = 144.2

1-(Pent-4-en-1-yl)-7-vinyl-1H-indole

Add sodium hydride (60% dispersion in mineral oil) (3.5 g, 87.3 mmol) to a 0°C solution of 7-vinylindole (5.0 g, 34.9 mmol) in 140 mL of dimethylformamide. Warm the resulting mixture to 20-24°C and stir an additional 30 minutes. Add 5-bromo-1-pentene (20 mL, 175 mmol) dropwise and stir for 3 hours. Pour the reaction mixture into a mixture of 150 mL of water and 150 mL of ethyl acetate. Wash the aqueous layer with ethyl acetate (3 x 100 mL). Combine the organic layers, wash with saturated aqueous sodium chloride, dry over sodium sulfate, filter, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 5-10% ethyl acetate in hexanes. Combine fractions containing product and concentrate them under reduced pressure to provide the desired compound as a clear oil (5.39 g, 73%).

MS (ES, m/z) C₁₅H₁₇N (M⁺+1) = 212

Ring Closure

Add 1.4 g of bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (Grubb's catalyst) to a solution of 1-(Pent-4-en-1-yl)-7-vinyl-1H-indole (4.4 g, 20.8 mmol) in anhydrous dichloromethane (3.0 L) and stir the resulting mixture at 20-24°C for 24 hours. Add an additional 1.0 g of Grubb's catalyst and stir for 4 hours. Concentrate the reaction mixture under reduced pressure and subject the residue to silica gel chromatography, eluting with 2-5% ethyl acetate in hexanes. Combine fractions containing product and concentrate them under reduced pressure to provide 8,9-dehydropyrrolo[3,2,1-kl]benzo[b]azacyclooctane as a brown oil (3.0 g, 79%).

¹H-NMR(400 MHz, DMSO-d₆): δ 7.41-7.39 (dd, 1 H, J = 7.81, 0.98 Hz), 7.22-7.21 (d, 1 H, J = 3.42 Hz), 6.94-6.9 (d, 1 H, J = 7.57 Hz), 6.81-6.8 (d, 1 H, J = 2.93 Hz), 6.79 (s, 1 H), 6.36-6.35 (d, 1 H, J = 2.93 Hz), 5.69-5.62 (m, 1 H), 4.45-4.3 (bs, 2 H), 2.19-2.14 (m, 2 H), 1.75-1.55 (bs, 2 H).

Reduction

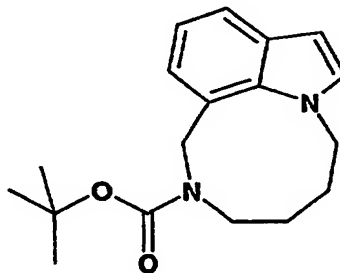
Hydrogenate a solution of 8,9-Dehydropyrrolo[3,2,1-kl]benzo[b]azacyclooctane (0.66 g, 3.6 mmol) in ethanol (130 mL) in the presence of platinum oxide (100 mg) under balloon pressure for three hours. Filter the mixture through Celite, wash solid with

dichloromethane, and concentrate the filtrate under reduced pressure to provide of the title compound as a light yellow oil (0.65 g, 97%).

MS (ES, m/z) $C_{13}H_{15}N$ ($M^+ + 1$) = 186

5

Preparation 18



8-(tert-butoxycarbonyl)-[1,5]diazaperhydroonino[8,9,1-hi]indole

N-Allyl N-[(1H-indol-7-yl)methyl]amine

10 Add allylamine (2.50 mL, 33.1 mmol), acetic acid (3.4 mL), and sodium triacetoxymethylborohydride (5.85 g, 27.6 mmol) to a solution of indole-7-carboxaldehyde (4.00 g, 27.6 mmol) in 1,2-dichloroethane (120 mL) at 20-24°C and stir the resulting mixture at 20-24°C for 5 hours. Add an additional 1.5 g (7.1 mmol) of sodium triacetoxymethylborohydride and stir the resulting mixture overnight. Dilute the mixture with dichloromethane (300 mL), wash carefully with aqueous sodium bicarbonate (100 mL),
15 and separate the layers. Wash the organic layer sequentially with water (100 mL) and saturated aqueous sodium chloride (100 mL), dry over sodium sulfate, filter, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 10-30% ethyl acetate in hexanes. Combine fractions containing product and concentrate them under reduced pressure to provide the desired compound as a light
20 yellow oil (4.21 g, 82%).

N-[tert-butoxycarbonyl] N-allyl N-[(1H-indol-7-yl)methyl]amine

Add a 0°C solution of di-tert-butyl dicarbonate (4.93 g, 22.6 mmol) in anhydrous tetrahydrofuran (20 mL) to a 0°C solution of N-allyl N-[(1H-indol-7-yl)methyl]amine
25 (4.21 g, 22.6 mmol) in anhydrous tetrahydrofuran (100 mL) and stir the mixture for two hours as it warms to 20-24°C. Dilute the reaction mixture ethyl acetate (500 mL).

Separate the phases and wash the organic layer sequentially with water (2 x 150 mL) and saturated aqueous sodium chloride (100 mL), dry over sodium sulfate, filter, and concentrate under reduced pressure to provide the desired compound as a light yellow oil (6.5 g, 100%).

5 MS (ES, m/z) $C_{17}H_{22}N_2O_2$ ($M^+ + 1$) = 287.2

N-[tert-butoxycarbonyl] N-allyl N-[(1-allyl-1H-indol-7-yl)methyl]amine

10 Slowly add sodium hydride (60% dispersion in mineral oil, 1.75 g, 43.7 mmol) to a 0 °C solution of N-[tert-butoxycarbonyl] N-allyl N-[(1H-indol-7-yl)methyl]amine (6.6 g, 23 mmol) in anhydrous dimethylformamide. Warm the mixture to 20-24°C, stir for 30 minutes, add allyl bromide (4.0 mL, 46 mmol), and stir the mixture at 20-24°C overnight. Dilute the reaction mixture with ethyl acetate (450 mL), wash sequentially with water (2 x 100 mL) and saturated aqueous sodium chloride (150 mL), dry over sodium sulfate, filter, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, 15 eluting with 10% ethyl acetate in hexanes. Combine fractions containing product and concentrate them under reduced pressure to provide the desired compound as a light brown oil (6.8 g, 91%).

MS (ES, m/z) $C_{20}H_{26}N_2O_2$ ($M^+ + Na$) = 349.2

20 Ring Closure

Beginning with N-[tert-butoxycarbonyl] N-allyl N-[(1-allyl-1H-indol-7-yl)methyl]amine, the ring closure was performed essentially as described in Preparation 17.

MS (ES, m/z) $C_{18}H_{22}N_2O_2$ ($M^+ + Na$) = 321.2

25

Reduction

Beginning with the alkene prepared in the previous paragraph, the double bond was reduced to provide the title compound essentially as described in Preparation 17.

MS (ES, m/z) $C_{18}H_{25}N_2O_2$ (M^+) = 301.2

30

Preparation 19

7-Bromofuro[3,2-c]pyridine

7-Bromo-5H-furo[3,2-c]pyridin-4-one

Add N-bromosuccinimide (63.16 g, 354.9 mmol) as a solution in anhydrous
5 acetonitrile (480 mL) to a suspension of 5H-furo[3,2-c]pyridin-4-one (36.9 g, 273 mmol)
in anhydrous acetonitrile (740 mL) at 0 °C over 1 hour. Warm to room temperature, add
anhydrous methyl alcohol (1.5 L) and stir at room temperature for 18 hours. Quench with
water (20 ml) and saturated sodium bicarbonate (20 mL), concentrate to a volume of 1.3
liters, and pour into water (1.3 L). Collection of the precipitate by filtration and drying
10 (vacuum oven 2 days 40-60 °C) gives the title compound as an off-white solid.
ESMS: (m/z) = 213.9, 215.9 (M^+ +1).

4,7-Dibromofuro[3,2-c]pyridine

Combine 7-bromo-5H-furo[3,2-c]pyridin-4-one (16.16 g, 75.5 mmol),
15 dichloroethane (160 mL), and phosphorus oxybromide (100 g, 348.8 mmol) and heat at
reflux for about 2 hours. Cool to room temperature and pour the reaction mixture into ice
water (1 L). Adjust the pH to 8 with 5N NaOH, extract into dichloromethane, wash with
brine, dry over magnesium sulfate, filter, and concentrate. Purification by flash
chromatography, eluting with hexane:ethyl acetate gives the title compound as a white
20 solid.
HRMS: 274.8581 (M^+).

Reduction

Combine 4,7-dibromofuro[3,2-c]pyridine (14.5 g, 52.3 mmol), anhydrous
25 dimethylformamide (250 mL), sodium formate (10.67 g, 156.9 mmol), and
tetrakis(triphenyl-phosphine)palladium(0) (3.021 g, 2.61 mmol) under nitrogen. Heat
for 3 to 24 hours at 100 °C, cool to room temperature, filter through CELITE® and
concentrate (high vacuum 0.7 mmHg, 40 °C). Dilute with ethyl acetate (500 mL),
wash with water and brine, dry over magnesium sulfate, filter and concentrate.
30 Purification by flash chromatography, eluting with hexane: ethyl acetate gives the title
compound as a white solid.
MS: (m/z) = 197.9, 199.9 (M^+ +1).

Preparation 20

5-Bromoimidazo[1,2-a]pyridine

Add 2-bromo-1,1-diethoxyethane (3.64 g, 18.48 mmol) to a solution of 6-bromopyridin-2-ylamine (1.0g, 5.77 mmol) in n-butanol (40 ml). Reflux the reaction overnight, cool. Filtration of the reaction mixture gives 5-bromoimidazo[1,2-a]pyridine hydrobromide as a white solid.

ESMS: (m/z) = 198.9 ($M^+ + 1$).

Add saturated sodium bicarbonate (300 ml) to a suspension of 5-bromoimidazo[1,2-a]pyridine hydrobromide (13.0g, 46.96 mmol) in ethyl acetate. Separate the organic layer and wash it with saturated sodium bicarbonate, dry over magnesium sulfate, and concentrated under reduced pressure to give the title compound as a white solid.

Preparation 21

5-Bromoisquinoline

Add a solution of sodium nitrite (9.6g, 139 mmol) in water (50 mL) cautiously to 5-aminoisquinoline (20 g, 139 mmol) in hydrobromic acid (48%, 100 mL) at 0°C.

Transfer this mixture to a vessel containing CuBr (25g, 174 mmol) in hydrobromic acid (48%, 200 mL) at 75 °C. After complete addition, stir the mixture at 75 °C for one hour, cool to room temperature and stir overnight. Place the mixture in an ice bath, add ice to the reaction mixture, and then add sodium hydroxide aqueous solution (20%, 250 mL). Filter the slurry and extract the filtrate with diethyl ether. Combine the solid and the extract sonicate for one hour in chloroform. Filter the suspension through a plug of Celite™, and concentrate the filtrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with chloroform.

MS(ES): m/z = 208.0 ($M^+ (^{79}\text{Br}) + 1$), 210.0 ($M^+ (^{81}\text{Br}) + 1$)

Preparation 22

(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)oxoacetic acid methyl ester

Add oxalyl chloride (1.05 mL, 12.08 mmol) dropwise to a solution of 5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline (1.67g, 10.6 mmol) in 150 mL of anhydrous diethyl ether at 0°C and stir the resulting solution at 0°C for 40 minutes. Cool the mixture to -78°C and

slowly add sodium methoxide (42 mL, 21 mmol, 0.5 M in methanol). Upon completion of the addition, remove the dry ice bath and allow the reaction to warm to 20-24°C over 2 hours. Dilute the mixture with ethyl acetate (200 mL), wash with water (100 mL) and separate the layers. Wash the organic layer with saturated aqueous sodium chloride (50 mL), dry over sodium sulfate, filter, and concentrate under reduced pressure. Dissolve the residue in ethyl acetate (100 mL), filter through a 2 inch plug of coarse silica gel, and concentrate under reduced pressure to give the title compound as a yellow solid (2.16 g, 84%).

MS (EI, m/z) $C_{14}H_{13}NO_3$ ($M^+ - 59$) = 184.

The compounds of Preparations 23 – 34 are prepared essentially as described in Preparation 22.

Prep.#	Compound	Data
23	(4,5,6,7-tetrahydroazepino[3,2,1-hi]indol-1-yl)oxoacetic acid methyl ester	MS (FIA, m/z) C ₁₅ H ₁₅ NO ₃ (M ⁺ +1) = 258.2
24	(6-(<u>tert</u> -butoxycarbonyl)-5,6-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)oxoacetic acid methyl ester	MS (IS, m/z) C ₁₆ H ₂₀ N ₂ O ₂ (M ⁺ +1) = 273
25	(Pyrrolo[3,2,1-kl]benzo[b]azacyclooct-1-yl)oxoacetic acid methyl ester	¹ H-NMR(400 MHz, DMSO-d ₆): δ 8.38(s, 1 H), 8.05-8.03(d, 1 H, J = 7.81 Hz), 7.18-7.15(t, 1 H, J = 7.57 Hz), 7.03-7.01(d, 1 H, J = 6.84 Hz), 4.65-4.62(t, 2 H, J = 6.1 Hz), 3.86(s, 3 H), 3.3-3.15(bs, 2 H), 1.94-1.91(t, 2 H, J = 6.1 Hz), 1.82-1.79(t, 2 H, J = 5.86 Hz), 1.3-1.15 (bs, 2 H)
26	(8-(<u>tert</u> -butoxycarbonyl)-[1,5]diazaperhydroonino[8,9,1-hi]indol-1-yl)oxoacetic acid methyl ester	MS (IS, m/z) C ₂₁ H ₂₆ N ₂ O ₅ (M ⁺ +1) = 387.
27	(6-(<u>tert</u> -butoxycarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)oxoacetic acid methyl ester	MS (IS, m/z) C ₂₀ H ₂₄ N ₂ O ₅ (M ⁺ +1)=373
28	(9-chloro-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)oxoacetic acid methyl ester	MS (IS m/z) C ₁₄ H ₁₂ ClNO ₃ (M+1) 278
29	(8-chloro-5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)oxoacetic acid methyl ester	MS (IS, m/z) C ₁₄ H ₁₂ ClNO ₃ (M+1) 277.8
30	(7-Fluoro-5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)oxoacetic acid methyl ester	MS (EI, m/z) C ₁₄ H ₁₂ FNO ₃ (M+1) 262.1
31	(8-Fluoro-5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)oxoacetic acid methyl ester	MS (EI, m/z) C ₁₄ H ₁₂ FNO ₃ (M+1) 262.1
32	6-(<u>tert</u> -butoxycarbonyl)-5-methyl-6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)oxoacetic acid methyl ester	MS (ES, m/z) (M + 1) = 373.0
33	9-methyl-6-(<u>tert</u> -butoxycarbonyl)-3,4-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indole	ESMS: m/z = 373 (M+1)
34	9-fluoro-6-(<u>tert</u> -butoxycarbonyl)-3,4-dihydro-6H-[1,4]diazepino[6,7,1-hi]indole	¹ H-NMR(CDCl ₃): δ 8.36(s, 1H), 8.02(d, 1H), 6.92 and 6.84(2 d, 1H), 4.89 and 4.80(2 s, 2H), 4.43(m, 2H), 3.98(m, 2H), 3.94(s, 3H), 1.46 and 1.42(2 s, 9H)

Preparation 35

(Imidazo[1,2-a]pyridin-5-yl)oxoacetic acid ethyl ester

Add Mg turnings (0.25 g, 9.95 mmol) to a solution of 5-Bromoimidazo[1,2-a]pyridine (1.5 g, 7.65 mmol) in tetrahydrofuran (20 ml). Heat the reaction to 60°C and add bromoethane (1.2 ml, 11.1 mmol). Reflux for another 0.5 hours, cool and cannula dropwise into a solution of diethyl oxalate (5 ml) in tetrahydrofuran (5ml) at -15°C. Stir at -15°C for 0.5 hours and at room temperature for 0.5 hours. Quench the reaction by adding pH 7 buffer, extract into ethyl acetate, wash with saturated sodium chloride, dry over magnesium sulfate, and concentrate under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate: hexane: methanol gradient gives the title compound as a light brown oil.

The compounds of Preparations 36 – 41 are prepared essentially as described in Preparation 35.

Prep.	Compound	Data
36	Methyl (benzofur-7-yl)oxoacetate	MS(ES): m/z = 218.9 (M+1)
37	Ethyl (4-methoxybenzofur-7-yl)oxoacetate	MS(ES): m/z = 248.9 (M+1)
38	Ethyl (5-methoxybenzofur-7-yl)oxoacetate	MS(ES): m/z = 249.0 (M+1)
39	Methyl (6-methoxybenzofur-7-yl)oxoacetate	¹ H-NMR(400 MHz, CDCl ₃): δ 1.41 (t, J = 7.31 Hz, 3H), 4.40 (m, 2H), 6.74(d, J = 1.95 Hz, 1H), 6.94(d, J = 8.78 Hz, 1H), 7.68(d, J = 2.44 Hz, 1H), 7.78(d, J = 8.23 Hz, 1H)
40	Ethyl (imidazo[1,2-a]pyridin-3-yl)oxoacetate	¹ H-NMR(400 MHz, DMSO-d ₆): δ 8.3(m, 1H), 7.53(m, 1H), 7.46 (s, 1H), 6.9(m, 1H), 6.42(m, 1H), 4.1(q, J = 7Hz, 2H), 1.15(t, J = 7Hz, 3H).
41	Ethyl (5-fluorobenzofur-7-yl)oxoacetate	ESMS: m/z = 237.0 (M+1)
42	Methyl (5-oxo-6-propyl-5,6-dihydro-[1,4]diazepino[6,7,1-hi]indol-7-yl)oxoacetate	¹ H-NMR(400 MHz, DMSO-d ₆): δ 8.58(s, 1 H), 8.05(m, 1H), 7.24-7.2(m, 2H), 5.35(m, 2H), 4.8(m, 2H), 3.8(s, 3H), 3.4 (m, 2H), 1.45(m, 2H), 0.7(m, 3H).

Preparation 43

(Imidazo[1,2-a]pyridin-3-yl)oxoacetic acid methyl ester

Add oxalyl chloride (2.13g, 1.46 ml, 16.8 mmol) to a solution of imidazo[1,2-a]pyridine (1.0 g, 8.47 mmol) in toluene (75 ml). Heat the mixture at reflux for 15 hours.

- 5 Cool the reaction and gently add methanol. Concentrate the resulting mixture under reduced pressure and partition between hot ethyl acetate and saturated aqueous sodium bicarbonate. Wash organic phase with saturated aqueous sodium chloride, dry over magnesium sulfate, and concentrate under reduced pressure. Triturate in ethyl acetate to give the title compound as an off-white solid (0.75 gm).

10 ESMS: $m/z = 204.9 (M^+ + 1)$

Preparation 44

(1-[3-(tert-Butyldimethylsilyloxy)prop-1-yl]-1H-indol-4-yl)oxoacetic acid methyl ester

- 15 Add tert-butyl lithium (88.1 ml, 149.8 mmol, 1.7 M in hexane) to a solution of 4-Bromo-1-[3-(tert-butyldimethylsilyloxy)propyl]-1H-indole (22.0g, 59.92 mmol) in anhydrous tetrahydrofuran (100 ml) at -78°C . Stir the reaction at -78°C for 20 min. Transfer the mixture into a solution of dimethyl oxalate (24.8g, 209.72 mmol) in tetrahydrofuran (400ml) at -40°C via a dry-ice cooled cannula. Upon complete addition, stir the reaction at -78°C for 15 minutes and slowly warm to room temperature. Quench
- 20 the reaction with saturated aqueous ammonium chloride and extract into ethyl acetate. Combine the organic layers, dry over magnesium sulfate, and concentrate under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate: hexane gradient (100% hexane to 15 % ethyl acetate: hexane over 90 minutes) gives the title compound, as a light brown oil.

25 ESMS: $m/z = 376.2 (M^+ + 1)$

The compounds of Preparations 45 – 47 are prepared essentially as described in Preparation 44.

Prep.	Product	Data
45	Methyl (1-methyl-1H-indol-4-yl)oxoacetate	HRMS: 218.0826(M+H)
46	Methyl (benzofur-7-yl)oxoacetate	HRMS: 205.0501 (M+H)
47	Methyl (isoquinolin-5-yl)oxoacetate	MS(ES): $m/z = 216.1 (M^+ + 1)$

Preparation 48

1-[3-(tert-butyldimethylsilyloxy)prop-1-yl]-1H-indole-4-carboxaldehyde

Add tert-butyl lithium (27.07 ml, 46.03 mmol, 1.7 M in pentane) to a solution of 4-Bromo-1-[3-(tert-butyldimethyl-silyloxy)prop-1-yl]-1H-indole (6.76 g, 18.41 mmol) in anhydrous tetrahydrofuran (100 ml) at -78°C . Stir the reaction at -78°C for 30 min, quench with N,N-dimethylform-amide (4.7 ml, 64.45 mmol), warm to 0°C , quench with pH = 7 buffer, and extract into ethyl acetate. Combine the organic layers, dry over magnesium sulfate, and concentrate under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate: hexane gradient (100% hexane to 50 % ethyl acetate: hexane over 45 minutes) gives the title compound as a clear oil.

ESMS: (m/z) = 318.2 ($M^{+}+1$)

The compounds of Preparations 49 – 52 are prepared essentially as described in Preparation 48.

Prep.	Compound	Data
49	1-Methyl-1H-indole-4-carboxaldehyde	HRMS: 160.0760 ($M+H$)
50	5-Fluorobenzofuran-7-carboxaldehyde	^1H NMR(400 MHz, DMSO- d_6): δ 10.25 (s, 1H), 8.25 (d, J = 2 Hz, 1H), 7.87 (dd, J = 8, 3 Hz), 7.65 (J = 8, 3 Hz), 7.1 (d, J = 2, 1H)
51	5,6-Difluorobenzofuran-7-carboxaldehyde	HRMS: 182.0179 (M^{+})
52	6-Fluorobenzofuran-7-carboxaldehyde	MS(ES): 165.0 (M^{+})

Preparation 53

Benzo[b]thiophene-7-carboxaldehyde

Dissolve 7-bromothiophene (5.0 g, 23.5 mmol) in anhydrous tetrahydrofuran (15 mL) under nitrogen and add magnesium metal turnings (712 mg, 29.3 mmol). Stir and warm the reaction to 50°C to initiate the Grignard reagent formation. After the exothermic reaction subsides, reflux for 30 minutes. Dilute the solution with tetrahydrofuran (15 mL) and cool to 25°C. Add the Grignard reagent dropwise via cannula to a stirred solution of N,N-dimethylformamide (10.2g, 139 mmol) in tetrahydrofuran (25 mL) at -78°C under nitrogen. Stir the reaction at 0°C for 1 hour and quench with aqueous saturated ammonium chloride. Dilute with diethyl ether, wash with distilled water, and aqueous saturated sodium chloride. Dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Chromatograph on flash silica using a gradient from neat hexane to 50% ethyl acetate in hexane to obtain the title compound as an off-white solid.

HRMS: 162.0138

The compounds of Preparations 54 – 60 are prepared essentially as described in Preparation 53.

Prep.	Compound	Data
54	4-Methoxybenzofuran-7-carboxaldehyde	¹ H NMR(400 MHz, DMSO-d ₆): δ 10.1 (s, 1H), 8.06 (s, 1H), 7.85 (d, J = 9 Hz, 1H), 7.04(m, 2H, 4.0 (s, 2H)
55	4-Fluorobenzofuran-7-carboxaldehyde	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.21 (s, 1H), 8.21 (d, J = 2 Hz, 1H), 7.89 (dd, J = 8, 8 Hz, 1H), 7.28 (dd, J = 8,8 Hz, 1H), 7.2 (d, J = 2 Hz, 1H)
56	4,5-Difluorobenzofuran-7-carboxaldehyde	HRMS: 182.0179 (M ⁺)
57	Benzo[b]thiophene-7-carboxaldehyde	HRMS: 162.0138 (M ⁺)
58	Benzo[b]thiophene-4-carboxaldehyde	HRMS: 162.0125 (M ⁺)
59	5-(tetrahydropyran-2-yloxy)benzofuran-7-carboxaldehyde	ESMS: (m/z) = 246.9 (M+1)
60	4-(tetrahydropyran-2-yloxy)benzofuran-7-carboxaldehyde	ESMS: (m/z)= 163.0 (M+1)

Preparation 61

Benzo[*b*]thiophene-7-acetonitrile

Add Benzo[*b*]thiophene-7-carboxaldehyde (2.34 g, 14.4 mmol) and lithium cyanide tetrahydrofuran complex (LiCN * 1.5 Tetrahydrofuran, 204 mg, 1.44 mmol) to
5 tetrahydrofuran (40 mL) under nitrogen. Add dropwise neat diethyl cyanophosphonate (2.8 mL, 18.4 mmol) to the stirring reaction mixture. Stir at room temp under nitrogen for 60 hours. Add 2-methyl-2-propanol (1.4 mL, 14.6 mmol). Add the reaction mixture via cannula to a stirred 0.1 molar solution of samarium(II) iodide in tetrahydrofuran (360 mL, 36.0 mmol) at 25°C under nitrogen. If the resulting reaction mixture is not deep blue add
10 additional samarium(II) iodide solution until deep blue color persists. Stir the reaction at 25°C for 1 hour. Concentrate under reduced pressure, dilute with ethyl acetate, diethyl ether (1:1), wash with aqueous 0.1 M hydrochloric acid, and aqueous saturated sodium chloride. Dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Chromatograph on flash silica using a gradient from
15 neat hexane to 25% ethyl acetate in hexane to obtain the title compound as an off-white solid.

HRMS: 173.0289 (M^+)

The compounds of Preparations 62 – 74 are prepared essentially as described in Preparation 61.

Prep.	Compound	Data
62	{1-[3-(<i>tert</i> -butyldimethylsilyloxy)-prop-1-yl]-1H-indol-4-yl}acetonitrile	¹ H-NMR(400 MHz, DMSO-d ₆): δ 7.43 (d, J = 8 Hz, 1H), 7.38(m, 1H), 7.14(m, 1H), 7.0(d, J = 8 Hz, 1H), 6.54(m, 1H), 4.23(t, J = 7, 2H), 4.18(s, 3H), 3.5(t, J= 7 Hz, 2H), 1.9 m, 2H), 0.85(s, 9H), 0.0(s, 6H)
63	(1-Methyl-1H-indol-4-yl)acetonitrile	HRMS: 171.0939 (M+H)
64	(1H-Indol-7-yl)acetonitrile	HRMS: 156.0687 (M ⁺)
65	(4-Methoxybenzofur-7-yl)acetonitrile	¹ H-NMR(400 MHz, DMSO-d ₆): δ 7.99 (d, J = 2 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 6.98 (d, J = 2 Hz, 1H) 6.8 (d, J = 8 Hz, 1H), 4.16 (s, 2H), 3.88 (s, 3H)
66	(5-Methoxybenzofur-7-yl)acetonitrile	¹ H-NMR(400 MHz, DMSO-d ₆): δ 8.02 (d, J = 2.2 Hz, 1H), 7.17(d, J = 2.2 Hz, 1H), 6.9(m, 2H), 4.24 (s, 3H)
67	(4-Fluorobenzofur-7-yl)acetonitrile	¹ H NMR(400 MHz, DMSO-d ₆): δ 8.15 (d, J = 2.2 Hz, 1H), 7.33 (m, 1H), 7.17-7.1 (m, 2H), 4.26 (s, 2H)
68	(4,5-Difluorobenzofur-7-yl)acetonitrile	¹ H NMR(400 MHz, DMSO-d ₆): δ 8.2 (d, J < 1 Hz, 1H), 7.42 (m, 1H), 7.22 (d, J < 1 Hz, 1H), 4.28 (s, 2H)
69	(5-Fluorobenzofur-7-yl)acetonitrile	¹ H NMR(400 MHz, DMSO-d ₆): δ 8.15 (d, J = 2 Hz, 1H), 7.47 (dd, J = 8, 2 Hz, 1H), 7.18 (dd, J = 8, 2 Hz, 1H), 7.01 (d, J = 2 Hz, 1H), 4.3 (s, 2H)
70	(5,6-Difluorobenzofur-7-yl)acetonitrile	ESMS (M ⁻ -1): 192.3
71	(6-Fluorobenzofur-7-yl)acetonitrile	¹ H-NMR(400 MHz, CDCl ₃): δ 7.62 (d, J = 2.44 Hz, 1H), 7.47 (m, 1H), 7.00 (m, 1H), 6.72 (d, J = 2.44 Hz, 1H), 3.91 (s, 2H)
72	(Benzo[b]thien-7-yl)acetonitrile	HRMS (M): 173.0289
73	(Benzofur-7-yl)acetonitrile	HRMS (M): 157.0524
74	(Benzo[b]thien-4-yl)acetonitrile	HRMS (M): 173.0288

Preparation 75

5

(Furo[3,2-c]pyridin-7-yl)acetonitrile

Furo[3,2-c]pyridine-7-carbonitrile

Combine 7-bromofuro[3,2-c]pyridine (4.673 g, 23.5 mmol), copper cyanide (4.21 g, 47.1 mmol), copper iodide (8.96 g, 47.1 mmol), and anhydrous dimethylformamide (100 mL) and at 130 °C for 30 hours. Cool to room temperature, dilute with diethyl ether

and wash with 15% aqueous ammonium hydroxide. Extract combined aqueous layers with diethyl ether, wash combined organic layers with 15% aqueous ammonium hydroxide, and brine, dry over magnesium sulfate, and concentrate. Purification using flash chromatography, eluting with hexane: ethyl acetate gives the title compound as a white solid.

ESMS: (m/z) = 145.1 ($M^+ + 1$)

Furo[3,2-c]pyridine-7-carboxylic acid

Add furo[3,2-c]pyridine-7-carbonitrile (1.5 g, 10.4 mmol) and 28-30% aqueous ammonium hydroxide (50 mL) to high pressure reactor. Heating at 150 °C for 18 hours, cooling to room temperature and freeze-drying gives the title compound as a white solid. ESMS: (m/z) = 164.0 ($M^+ + 1$).

(Furo[3,2-c]pyridin-7-yl)methanol

Add Borane (1.0 M in tetrahydrofuran, 0.61 mL, 0.61 mmol) to a solution of furo[3,2-c]pyridine-7-carboxylic acid (0.100g, 0.61 mmol) in tetrahydrofuran (2 mL) and stir for 1 hour. Add additional borane (0.61 mL) stir for 30 minutes, add additional borane (0.61 mL), quench with 1N HCl (10 mL) and stir for 15 minutes. Add aqueous ammonium hydroxide (28-30%, 3 mL), extract with diethyl ether, dry over magnesium sulfate, filter and concentrate to give the title compound as a white solid. ESMS: (m/z) = 150.1 ($M^+ + 1$)

Conversion of alcohol to nitrile

Combine (furo[3,2-c]pyridin-7-yl)methanol (0.40 g, 2.68 mmol), 1N HCl (1.0 M in diethyl ether, 3 mL). Cool to 0 °C and add thionyl chloride (5 mL). Heat at reflux for 2 hours, cool to room temperature and concentrate to the white solid 7-(chloromethyl)furo[3,2-c]pyridine hydrochloride. Dissolve in ethanol (4.4 mL) and water (1.7 mL) and introduce drop wise a refluxing solution of sodium cyanide (0.656 g, 13.4 mmol) in ethanol (5.4 mL) and water (1 mL) over 40 minutes. Heat for 40 minutes at reflux, cool to room temperature, dilute with water, and extract with ethyl acetate. Combine organic layers, wash with brine, dry over magnesium sulfate, filter and

concentrate. Purification by flash chromatography, eluting with hexane:ethyl acetate gives the title compound.

ESMS: (m/z) = 159.0 ($M^+ + 1$)

5

Preparation 76

(2,3-Dihydrobenzo[1,4]dioxin-5-yl)acetonitrile

(2,3-Dihydrobenzo[1,4]dioxin-5-yl)methanol

Dissolve 2,3-Dihydroxybenzaldehyde (25 g, 181 mmol) and 1,2-dibromoethane (34 g, 181 mmol) in N,N-dimethylformamide (500 mL). Add cesium carbonate (118 g, 362 mmol), stir and reflux under nitrogen for 2 hours. Cool the reaction to 20°C, dilute with absolute ethanol (250 mL) and add sodium borohydride (6.8 g, 181 mmol). Stir at 20°C for 1 hour and concentrate under high vacuum to remove the ethanol and dimethylformamide. Dilute the residue with diethyl ether and wash with distilled water, 0.25 molar aqueous sodium hydroxide, and aqueous saturated sodium chloride. Dry the organic phase over anhydrous magnesium sulfate, filter and concentrate under reduced pressure. Chromatograph on flash silica using a gradient from 75% hexane, 25% ethyl acetate to 25% hexane, 75% ethyl acetate to obtain the title compound as a white solid. HRMS: 166.0621 (M)

20

Halogenation/Displacement

Beginning with (2,3-dihydrobenzo[1,4]dioxin-5-yl)methanol (1.8 g, 10.8 mmol), the title compound is prepared essentially as described in Preparation 75.

HRMS: 175.0624 (M^+)

25

Preparation 77

(5-hydroxybenzofur-7-yl)acetonitrile

7-bromo-5-(tetrahydropyran-2-yloxy)benzofuran

Combine 7-bromo-5-hydroxybenzofuran (5.0 g, 0.0235 mol) with pyridinium para-toluenesulfonate (0.59 g, 0.1 equivalent) and dissolve in 60 mL dichloromethane under nitrogen. Add via syringe 3,4-dihydro-2H-pyran (3.2 mL, 1.5 equivalents) and stir at 20° C overnight. Dilute with dichloromethane then extract with 1N sodium hydroxide

30

and wash with brine. Dry over sodium sulfate, filtered, and then concentrate to afford the title compound as a brown oil.

^1H NMR(400 MHz, CDCl_3): δ 1.70(m, 6H), 3.57(m, 1H), 3.86(m, 1H), 5.31(t, $J = 3.17$ Hz, 1H), 6.69(d, $J = 2.20$ Hz, 1H), 7.19(m, 2H), 7.58(d, $J = 2.20$ Hz, 1H).

5

[5-(tetrahydropyran-2-yloxy)benzofur-7-yl]acetonitrile

Combine 5-(tetrahydropyran-2-yloxy)benzofuran-7-carboxaldehyde (3.75 g, 0.015 mol) with lithium cyanide-tetrahydrofuran (1:1.5 complex, 0.215 g, 0.1 equivalent) in tetrahydrofuran (80 mL) under nitrogen. Add diethyl cyanophosphonate (3.0 mL, 1.3 equivalents) and stir at 20° C for 2 days. Add tert-butanol (1.6 mL, 1.1 equivalents) then SmI_2 in tetrahydrofuran (0.1 M solution, approximately 400 mL). Concentrate the solution in vacuo then redissolve in a solution of ethyl acetate:diethyl ether (approximately 3:1, 100 mL). Add saturated aqueous ammonium chloride and stir for 20 min, until the release of hydrogen cyanide is complete. Filter to remove insoluble material, then extract against 1 N hydrochloric acid. Dry over sodium sulfate, then filter and concentrate. Purification by a plug column (4:1 hexanes:ethyl acetate) to provide the title compound as a light yellow oil.

^1H NMR(400 MHz, CDCl_3): δ 1.70(m, 6H), 3.54(m, 1H), 3.88(m, 1H), 3.91(s, 2H), 5.34(t, $J = 3.17$ Hz, 1H), 6.67(d, $J = 2.20$ Hz, 1H), 7.01(d, $J = 1.95$ Hz, 1H), 7.20(d, $J = 2.44$ Hz, 1H), 7.55(d, $J = 2.20$ Hz, 1H).

Deprotection

Dissolve [5-(tetrahydropyran-2-yloxy)benzofur-7-yl]-acetonitrile (3.89 g, 0.015 mol) in methanol (100 mL) and add para-toluenesulfonic acid monohydrate (0.288 g, 0.1 equivalent). After 20 minutes extract with ethyl acetate against water, then wash with brine. Concentration in vacuo affords the title compound as an off-white solid.

HRMS: Calculated: 173.0465. Found: 173.0477.

Preparation 78

(4-Hydroxybenzofur-7-yl)acetonitrile

Beginning with 4-(Tetrahydropyran-2-yloxy)benzofuran-7-carboxaldehyde, the title compound is prepared essentially as described in Preparation 77.

ESMS: $m/z = 172.0$ ($M-1$)Benzo[*b*]thiophene-7-acetamide

Add benzo[*b*]thiophene-7-acetonitrile (1.9 g, 11.0 mmol) to 2-methyl-2-propanol (20 mL). Heat to reflux under nitrogen and add potassium hydroxide pellets (7.4 g, 132 mmol). Stir and reflux under nitrogen for 30 minutes. Pour solution off of the excess potassium hydroxide and dilute with ethyl acetate. Wash with a 1:1 mixture of aqueous saturated sodium chloride, aqueous saturated sodium hydrogen carbonate. Dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Rinse the solid with cold diethyl ether and dry under vacuum to obtain the title compound as an off-white solid.

HRMS: 192.0483 ($M^+ + H$)

The compounds of Preparations 80 – 94 are prepared essentially as described in Preparation 79.

Prep.	Product	Data
80	2-(1-Methyl-1H-indol-4-yl)acetamide	HRMS: 189.1028 ($M+H$)
81	2-(1H-Indol-7-yl)acetamide	1H -NMR(400 MHz, DMSO- d_6) δ 10.9 (bs, 1H), 7.44-7.37(m, 2H), 7.32(dd, $J = 2, <1$), 6.98-6.91 (m 3H), 6.41(m, 1H), 3.62 (s, 2H)
82	2-(4-Methoxybenzofur-7-yl)acetamide	MS(ES): 206.0 ($M^+ + 1$)
83	2-(5-Methoxybenzo-fur-7-yl)acetamide	1H -NMR(400 MHz, DMSO- d_6) δ 7.91 (d, $J = 2$ Hz, 1H), 7.5 (bs, 1H), 7.1 (d, $J = 2$ Hz, 1H), 6.96 (bs, 1H), 6.85 (d, $J = 2$ Hz, 1H) 6.8 (d, $J = 2$ Hz, 1H), 3.74 (s, 3H), 3.61 (s, 2H)
84	2-(4-Fluorobenzofur-7-yl)acetamide	HRMS: 194.0617 ($M^+ + 1$)
85	2-(4,5-Difluoro-benzofur-7-yl)acetamide	1H -NMR(400 MHz, DMSO- d_6) δ 8.1 (d, $J = 2$ Hz, 1H), 7.55 (bs, 1H), 7.27 (m, 2H), 7.14(d, $J = 2$ Hz, 1H), 7.01 (bs, 1H), 3.65 (s, 2H)
86	2-(5-Fluorobenzofur-7-yl)acetamide	MS(ES): 194.1 ($M^+ + 1$)
87	2-(5,6-Difluorobenzo-fur-7-yl)acetamide	1H -NMR(400 MHz, DMSO- d_6) δ 8.08 (d, $J = 2.2$, 1H), 7.63 (bs, 1H), 7.59 (dd, $J = 8, 8$ Hz, 2H), 7.09 (bs, 1H), 6.9 (d, $J = 2.2$ Hz, d), 3.75 (s, 3H)
88	2-(6-Fluorobenzofur-7-yl)acetamide	MS(ES): $m/z = 194.0$ ($M^+ + 1$)

89	2-(Benzo[b]thien-7-yl)acetamide	HRMS: 192.0483 ($M^+ + H$)
90	2-(Benzofur-7-yl)acetamide	HRMS: 176.0717 ($M^+ + H$)
91	2-(Benzo[b]thien-4-yl)acetamide	HRMS: 192.0490 ($M^+ + H$)
92	2-(Furo[3,2-c]pyridin-7-yl)acetamide	MS(ES): $m/z = 177.1$ ($M^+ + 1$)
93	2-(2,3-Dihydrobenzo[1,4]dioxin-5-yl)-acetamide	HRMS: 194.0810 ($M + H$)
94	2-{4-[3-(<i>tert</i> -Butyldimethyl-silyloxy)-propoxy]benzofur-7-yl}acetamide	MS(ES): $m/z = 364.2$ ($M^+ + 1$)
95	2-(1,3-dihydroisobenzofur-5-yl)acetamide	MS(ES): $m/z = 178.1$ ($M^+ + 1$)

Preparation 96

(5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)acetamide(5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)oxoacetamide

5 Add concentrated ammonium hydroxide (2 mL) to a solution of (5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)oxoacetic acid methyl ester (0.50 g, 2.06 mmol) in 10 mL of tetrahydrofuran at 0°C. Remove the cooling bath and stir the mixture for 3 hours.

Dilute the reaction with 20 mL of water and filter the suspension. Wash the filter cake with 10 mL of water followed by 10 mL of diethyl ether, and dry under reduced pressure to provide the desired compound as a light yellow solid (0.403 g, 86%).

10 MS (IS, m/z) $C_{13}H_{12}N_2O_2$ ($M^+ + 1$) = 229

Reduction

15 Add 10% palladium on carbon (0.060 g) followed by the careful addition of $NaH_2PO_2 \cdot H_2O$ (0.60 g, 5.67 mmol) to a solution of (5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)oxoacetamide (0.30 g, 1.31 mmol) in dioxane (6 mL) and water (2 mL) and reflux the reaction under nitrogen. After 3 hours add 0.60 g of $NaH_2PO_2 \cdot H_2O$ and reflux for 6 hours. Cool the mixture, filter through Celite, and wash with ethyl acetate (100 mL). Concentrate the filtrate under reduced pressure and treat the residue with water (20 mL). Filter the resulting suspension and dry the recovered solid dried under reduced pressure to provide the title compound as a white solid (0.27 g, 96%).

20 MS (IS, m/z) $C_{13}H_{14}N_2O_1$ ($M^+ + 1$) = 215

Preparation 97

2-(6-(tert-butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)acetamide

Beginning with (2-(6-(tert-butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)oxoacetic acid methyl ester (5.0g, 13.95 mmol), the title compound is

5 prepared essentially as described in Preparation 94.

MS (ES, m/z): $C_{18}H_{23}N_3O_3$: 330.3 ($M^+ + 1$), 328.4 ($M^+ - 1$)

Preparation 98

2-(Benzofur-4-yl)acetamide

10 Add 1,1'-carbonyldiimidazole (2.3 g, 14.2 mmol) to a solution of 2-(benzofur-4-yl)acetic acid (2.5g, 14.2 mmol) in anhydrous tetrahydrofuran (12 mL) under nitrogen and stir at 20°C for 4 hours. Bubble anhydrous ammonia through the solution, dilute with anhydrous tetrahydrofuran (10 mL) and stir at 20°C for 18 hours. Concentrate under reduced pressure, wash the solid with aqueous sodium hydrogen sulfate, distilled water,
15 and dry under vacuum to obtain the title compound as a pale yellow solid.

ESMS: m/z = 176.1 ($M^+ + 1$)

Preparation 99

2-(Imidazo[1,2-a]pyridin-3-yl)acetamide

20 Add ethyl (E)-oxybutenoate (14.3g, 111.66 mmol) to 2-aminopyridine (10.0 g, 106.4 mmol) in acetonitrile (270 ml). Heat the reaction at 80°C for 6 hours. Concentrate the reaction mixture under reduced pressure. Purify the resulting oil by flash chromatography, eluting with a gradient of 100% hexane to 95% ethyl acetate: methanol to provide imidazo[1,2-a]pyridin-3-yl-acetic acid ethyl ester (10.95g, 50.0%) as a brown
25 solid.

1H -NMR(400 MHz, DMSO- d_6): δ 8.3 (m, 1H), 7.53 (m, 1H), 7.46 (s, 1H), 6.9 (m, 1H), 6.42 (m, 1H), 4.1 (q, J = 7Hz, 2H), 1.15 (t, J = 7Hz, 3H)

Bubble ammonia through a solution of (imidazo[1,2-a]pyridin-3-yl)acetic acid ethyl ester (10.0 g, 48.96 mmol) in methanol (30 ml) at 0°C. Heat the reaction mixture in
30 a sealed tube at 100°C for 2 hours. Concentrate the reaction mixture under reduced pressure. Triturate with ethyl acetate to give the title compound as a white solid.

ESMS: m/z = 176.1 ($M^+ + 1$)

Preparation 100

(5-oxo-6-propyl-5,6-dihydro-[1,4]diazepino[6,7,1-hi]indole

(1H-Indol-7-ylmethyl)propylamine

Add propyl amine (3.66 g, 62.07 mmol) to a solution of indole-7-carboxaldehyde (3.0 g, 20.68 mmol) and acetic acid (2.65 ml, 41.3 mmol) in toluene (100 ml). Heat at reflux constantly removing water with a Dean Stark apparatus. Concentrate the reaction under reduced pressure and re-dissolve in methanol. Gently add sodium borohydride (0.39 g, 10.34 mmol). Stir for 1 hour at room temperature, concentrate, and partition between ethyl acetate and saturated aqueous sodium bicarbonate. Concentrate the organic layers under reduced pressure. Compound carried onto next step without purification. ¹H NMR (400 MHz, CDCl₃) δ 10.9 (bs, 1 H), 7.4 (d, *J* = 8 Hz, 1H), 7.28 (d, *J* = 1.5 Hz, 1H), 7.0 (d, *J* = 7 Hz, 1H), 6.1 (dd, *J* = 8.06, <1 Hz, 1H), 6.4 (d, *J* = 1.5 Hz, 1H), 3.95 (s, 1 H), 2.5 (t, *H* = 7 Hz, 2 H), 1.45 (m, 2 H), 0.8 (t, *J* = 7 Hz, 3H).

Ring Formation

Add chloroacetyl chloride (1.7 ml, 21.71 mmol) and diisopropylethylamine (10.38 ml, 62.04 mmol) to a solution of (1H-Indol-7-ylmethyl)propylamine (3.89 g, 20.68 mmol) in methylene chloride. Stir for 2 hours, quench with saturated aqueous ammonium chloride and extract into ethyl acetate. Wash the organic layers with saturated aqueous sodium chloride, dry over magnesium sulfate, filter, and concentrate under reduced pressure to yield N-(1H-indol-7-yl)methyl N-propyl 2-chloroacetamide (5.47 gm, 20.68 mMol).

Add 5.47 gm (20.68 mMol) N-(1H-indol-7-yl)methyl N-propyl 2-chloroacetamide to a suspension of sodium hydride (10 gm, 60% dispersion in mineral oil) in 350 mL dimethylformamide and stir the reaction at room temperature. Once starting material is consumed concentrate the reaction mixture under reduced pressure. Dissolve the residue in ethyl acetate, wash sequentially with water and saturated aqueous sodium bicarbonate. Subject to silica gel chromatography to provide the title compound (3.15 gm, 69%). ESMS: 229.1 (M⁺+1).

Preparation 101

4-Bromo-1-[2-(*tert*-butyldimethylsilyloxy)eth-1-yl]-1H-indole

Add sodium hydride (4.89g, 122.4 mmol, 60% dispersion in mineral oil) to a solution of 4-Bromo-1H-indole (12g, 61.2 mmol) in dimethylformamide (100 ml). Cool the reaction to 0°C and add (2-bromo-1-(*tert*-butyldimethylsilyloxy)ethane (17.04 g, 67.32 mmol). Stir the reaction for 1 hour at room temperature, quench with aqueous saturated sodium bicarbonate, and extract into ethyl acetate. Combine the organic layers and wash with saturated aqueous sodium chloride, dry over magnesium sulfate. Concentrate under reduced pressure to obtain the title compound, as a clear oil.

¹H-NMR(400 MHz, DMSO-d₆): δ 7.48 (d, J = 8, 1H), 7.4(d, J = 3Hz, 1H), 7.22(d, J = 8 Hz, 1H), 7.05 (dd, J = 8, 1Hz, 1H), 6.4 (d, J= 3Hz, 1H), 4.25 (t, J = 7 Hz, 2H), 3.49(t, J = 7 Hz, 2H), 1.9 (quintuplet, 2H), 0.82 (s, 9H), 0.0 (s, 6H).

The compounds of Preparations 102 – 105 are prepared essentially as described in Preparation 101.

Prep.	Compound	Data
102	4-Bromo-1-[3-(<i>tert</i> -butyldimethylsilyloxy)prop-1-yl]-1H-indole	¹ H-NMR(400 MHz, DMSO-d ₆): δ 7.48(d, J = 8, 1H), 7.4(d, J = 3Hz, 1H), 7.22(d, J = 8 Hz, 1H), 7.05(dd, J = 8, 1Hz, 1H), 6.4(d, J= 3Hz, 1H), 4.25(t, J = 7 Hz, 2H), 3.49(t, J = 7 Hz, 2H), 1.9 (quintuplet, 2H), 0.82(s, 9H), 0.0(s, 6H)
103	4-Bromo-1-methyl-1H-indole	¹ H-NMR(400 MHz, CDCl ₃): δ 7.29-7.25(m, 2H), 7.10(d, J = 3.2Hz, 1H), 7.07(d, J = 8 Hz, 1H), 6.53(d, J = 2.4Hz, 1H), 3.79(s, 3H)
104	1-[2-(<i>tert</i> -butyldimethylsilyloxy)-eth-1-yl]-6-methoxy-1H-indole	HRMS (M ⁺ +1): 306.1882
105	7-Bromo-1-(but-3-enyl)-1H-pyrrolo[2,3-c]pyridine	MS(ES+): 251.3 [M(⁷⁹ Br)+1] ⁺ , 253.3 [M(⁸¹ Br)+1] ⁺

Preparation 106

(6-Methanesulfonyl-5,6-dihydro-[1,4]diazepino[6,7,1-hi]indol-1-yl)oxoacetic acid methyl ester

6-Methanesulfonyl-5,6-dihydro-[1,4]diazepino[6,7,1-hi]indole

Add triethylamine (3.19 g, 31.56 mmol) to a solution of 2-[(1H-Indol-7-ylmethyl)amino]-ethan-1-ol (2.0 g, 10.52 mmol) in tetrahydrofuran (50 ml) at 0°C.

Slowly add 1.75 mL (22.09 mMol) methanesulfonyl chloride and allow the reaction to warm to room temperature. Quench the reaction with saturated aqueous sodium bicarbonate and extract into ethyl acetate. Combine the organic layers, wash sequentially with saturated aqueous ammonium chloride, water, and saturated aqueous sodium chloride, dry over magnesium sulfate, and concentrate under reduced pressure. Add sodium hydride (0.8416 g, 21.04 mmol, 60% dispersion in mineral oil) to the resulting oil in dimethylformamide (20 ml). Quench the reaction with saturated aqueous sodium bicarbonate, concentrate to about 10 ml and extract into ethyl acetate. Combine the organic layers, wash sequentially with saturated ammonium chloride, water, and saturated aqueous sodium chloride, dry over magnesium sulfate, and concentrate under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate: hexane gradient gives the title compound as an off-white solid.

Oxoacetic acid formation

Beginning with 6-methanesulfonyl-5,6-dihydro[1,4]diazepino[6,7,1-hi]indole (1.47 g, 5.89 mmol), the title compound (1.1 gm, 56%) is prepared essentially as described in Preparation 22
ESMS ($M^+ + 1$): 337.1

Preparation 107

2-(4-(acetylamino)benzofur-7-yl)acetamide

2-(2,2-Dimethoxyethoxy)-1-methyl-4-nitrobenzene

Add bromoacetaldehyde dimethylacetal (30.3 g, 179 mmol) to 2-methyl-5-nitrophenol (25 g, 163 mmol) and potassium carbonate (50 g, 362 mmol) in dimethylformamide (200 mL). Stir and reflux under nitrogen for 2.5 hours. Cool to 20°C temperature and add aqueous sodium hydroxide (200 mL, 1 M). Dilute the mixture with hexane, diethyl ether (1:1), wash with 0.2 M aqueous sodium hydroxide, aqueous saturated sodium chloride, dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Recrystallize the product from hexane to obtain the desired compound, as tan colored solid 30.6 gm (77%).

7-Methyl-4-nitro-benzofuran

Add Amberlyst® 15 ion-exchange resin (36 g) to chlorobenzene (700 mL). Heat the reaction mixture to reflux and azeotrope out water, to dry the resin. Dissolve 2-(2,2-dimethoxyethoxy)-1-methyl-4-nitrobenzene (34.8 g, 144 mmol) in chlorobenzene (125 mL) and add dropwise to the stirring, refluxing reaction mixture under nitrogen over 15 minutes. Continue refluxing for 1.5 hours. Cool to room temperature, filter to remove the resin and concentrate under reduced pressure. Dissolve the residue in hexane, diethyl ether (1:1), wash with 0.5 M aqueous sodium hydroxide, aqueous saturated sodium chloride, dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Chromatograph on flash silica using hexane, ethyl acetate (9:1) and recrystallize from hexane, toluene (1:1) to obtain the desired compound as a yellow solid (9.7 g, 42%).

N,N-[Dimethyl] (2-(4-nitrobenzofur-7-yl)vinyl)amine

Add 7-methyl-4-nitro-benzofuran (3.5 g, 19.7 mmol) to tert-butoxy bis(dimethyl-amino)methane (10.3 g, 59.1 mmol). Reflux under nitrogen for 40 minutes. Concentrate under reduced pressure. Dissolve in xylenes (50 mL), concentrate under reduced pressure and dry under vacuum to obtain the desired compound as a deep red-brown solid (4.9 g, 100%).

HRMS: 233.0928 (M+H)

(4-Nitrobenzofur-7-yl)acetonitrile

Add N,N-[dimethyl] (2-(4-nitrobenzofur-7-yl)vinyl)amine (4.8 g, 20.6 mmol) and hydroxylamine-O-sulfonic acid (4.6 g, 40.6 mmol) to dimethylformamide (45 mL) and stir the mixture at room temperature for 15 minutes. Heat at 100°C under nitrogen for 1 hour. Cool to room temperature, dilute with diethyl ether, wash with water, aqueous saturated sodium chloride, dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Chromatograph on flash silica using 85% hexane, 15% ethyl acetate to obtain the desired compound as a light brown solid (2.9 g, 64%).

ESMS: m/z = 200.9 (M-1)

N-[7-(Cyanomethyl)benzofur-4-yl]acetamide

Add (4-Nitrobenzofur-7-yl)acetonitrile (600 mg, 2.96 mmol), acetic anhydride (600 mg, 5.88 mmol), and 5% palladium on carbon (300 mg) to tetrahydrofuran (25 mL). Stir under 1 atmosphere of hydrogen for 45 minutes. Dilute with ethyl acetate, filter through a pad of Celite®, concentrate under reduced pressure, and chromatograph on flash silica using 75% ethyl acetate, 25% hexane to obtain the desired compound as an off-white solid (0.43 gm, 67%).

HRMS: 215.0816 (M+H)

Nitrile Hydrolysis

Dissolve N-[7-(Cyanomethyl)benzofur-4-yl]acetamide (300 mg, 1.40 mmol) in 2-methyl-2-propanol (15 mL). Heat to reflux under nitrogen and add potassium hydroxide pellets (1.50 g, 26.7 mmol). Stir and reflux under nitrogen for 30 minutes. Pour solution off of the excess potassium hydroxide and dilute with ethyl acetate. Wash with aqueous saturated sodium chloride, aqueous saturated sodium hydrogen carbonate (3:1), dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Rinse the solid with cold ethyl acetate, cold methanol and dry under vacuum to obtain the title compound as a tan solid (160 mg, 49%).

HRMS: 255.0733 (M+H)

Preparation 108

2-(thieno[3,2-b]pyridin-7-yl)acetamide

7-Bromo-thieno[3,2-b]pyridine

Heat phosphorus oxybromide (145.00 g, 0.50 moles) to 60 °C to form a melt. Add thieno[3,2-b]-7-pyridinol (14.73 g, 97.43 mmol) while stirring and increase heat to 100 °C for 2 hours. Pour the reaction contents over ice (1.0 kg). Dilute the slurry with ice and water to about 3 L. Extract the aqueous solution with chloroform (4 X 500 mL). Make the aqueous solution basic (pH 10-11) with 2 N sodium hydroxide and reextract with chloroform (3 X 400 mL). Treat the organic layers with magnesium sulfate, filter and concentrate. Redissolve the crude solid in dichloromethane (100 mL) and load the solution onto silica (300 g). Elute with 2 L of 30% ethyl acetate/dichloromethane.

Concentrate the eluent to yield the desired compound as a crystalline solid (18.68 g, 89.5%).

2-Thieno[3,2-*b*]pyridin-7-yl-malonic acid diethyl ester

5 Charge a flask containing sodium hydride (17.45 g, 0.44 moles) with anhydrous dioxane (500 ml) while cooling at 0 °C. Add diethyl malonate (69.88 g, 0.44 moles) dropwise over one hour. Upon reaching ambient temperature, add copper (I) bromide (62.59 g, 0.44 moles). Add 7-bromothieno[3,2-*b*]pyridine (18.68 g, 87.26 mmol) as a solution in dioxane (50 mL). Heat the reaction to reflux for 18 hours. Concentrate the
10 reaction solution to ~175 mL. Pour the concentrate into concentrated ammonium hydroxide (2.5 L). Extract the aqueous phase with ethyl acetate (6 X 300 mL). Wash the organic layers exhaustively with 2 N sodium hydroxide until the blue color dissipates. Treat the organic layers with magnesium sulfate, filter and concentrate. Purification on silica utilizing a solution of 1:1:3 of ether, ethyl acetate and hexane as eluent yields the
15 desired compound (14.6 gm, 57%).

(Thieno[3,2-*b*]pyridin-7-yl)acetic acid ethyl ester

Dissolve 2-(thieno[3,2-*b*]pyridin-7-yl)malonic acid diethyl ester (12.90 g, 44.0 mmol) in dimethyl sulfoxide (295 mL). Add water (0.79 mL) and lithium chloride (3.73
20 g, 87.9). Heat the solution to 110 °C for 3 hours. Quench the reaction with saturated brine (3 L) and extract with ethyl acetate (3 X 1 L). Rewash the organic layers with saturated brine (1 L). Treat the organic layers with magnesium sulfate, filter and concentrate. The residue was purified on silica using 25% ethyl acetate/hexanes to yield the desired compound (5.25 g, 54%).

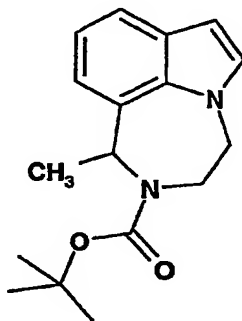
2-(Thieno[3,2-*b*]pyridin-7-yl)acetamide

25 In a high pressure flask, dissolve (thieno[3,2-*b*]pyridin-7-yl)acetic acid (3.02 g, 13.65 mmol) in absolute ethanol (100 mL). Add ammonium chloride (1.09 g, 20.38 mmol) to the solution. Cool the solution to -78 °C. Condense ammonia gas into the
30 solution by bubbling (15 minutes at 10 psi). Seal the flask and slowly bring to ambient temperature. Stir the reaction at room temperature for 4 days. Cool the reaction vessel to -78 °C. Open the flask and allow it to slowly return to ambient pressure. Filter the

contents and wash with water (10 mL) to obtain the title compound as a white solid (1.46 g). Concentrate the filtrate and triturate the residue with diethyl ether. Filter and wash with water (5 mL) to obtain additional pure product (0.46 g).

5

Preparation 109



6-(tert-butoxycarbonyl)-7-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indole
N-[tert-butoxycarbonyl]-N-[2-hydroxyeth-1-yl] 7-(1-aminoeth-1-yl)indole

10 Dissolve 7-formylindole (2.5 g, 17.2 mmol), 2-aminoethanol (1.31 g, 21.4 mmol), and glacial acetic acid (1.29 g, 21.4 mmol) in toluene (250 mL). Reflux for 30 minutes and remove the water using a Dean-Stark trap. Distill some of the toluene (200 mL) from the reaction mixture and cool the reaction to 0°C. To the stirring reaction at 0°C add dropwise 1.5 molar methyllithium-lithium bromide complex in diethyl ether (57 mL, 85.5 mmol) under nitrogen. Stir the reaction at 0°C for 15 minutes and quench by adding
15 saturated aqueous sodium hydrogen carbonate (125 mL). Add a solution of di-tert-butyl dicarbonate (7.52 g, 34.4 mmol) in tetrahydrofuran (50 mL) and stir at 20°C for 18 hours. Add aqueous ammonia (29%, 15 mL), dilute the reaction with ethyl acetate, wash the organic layer sequentially with distilled water and saturated aqueous sodium chloride. Dry the organic layer over anhydrous magnesium sulfate, filter, concentrate under reduced
20 pressure and chromatograph on flash silica using ethyl acetate in hexane to obtain 2.5 g (47%) of the desired compound as a colorless oil.

HRMS: $m/z = 327.1677$ (M+Na)

Ring Formation

Add N-[tert-butoxycarbonyl]-N-[2-hydroxyeth-1-yl] 7-(1-aminoeth-1-yl)indole (2.5 g, 8.21 mmol) to a solution of triethylamine (2.5 g, 24.7 mmol) and anhydrous dimethylformamide (40 mL) and cool to 0°C under nitrogen. Add a solution of methanesulfonic anhydride (1.80 g, 10.3 mmol) in dimethylformamide (10 mL) dropwise and stir at 0°C for 30 minutes. Dilute the reaction mixture with cold (0°C) anhydrous dimethylformamide (200 mL) and hexane (50 mL). Add sodium hydride 60% dispersion in mineral oil (1.97 g, 49.2 mmol), to the stirring reaction mixture under nitrogen, and allow the reaction to slowly warm to 20°C. Stir at 20°C for 18 hours. Quench the excess sodium hydride by adding 50% aqueous acetic acid (20 mL) and concentrate under reduced pressure. Dilute the residue with diethyl ether, ethyl acetate (1:1), wash with distilled water, 0.5 molar aqueous sodium hydrogen carbonate and aqueous saturated sodium chloride. Dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Chromatograph on flash silica using ethyl acetate in hexane to obtain 2.2 g (94%) of the title compound as a white solid.

HRMS: $m/z = 309.1579$ (M+Na)

Preparation 110

6-(tert-butoxycarbonyl)-7-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)oxoacetic acid methyl ester

Beginning with 6-(tert-butoxycarbonyl)-7-methyl-6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indole, the title compound was prepared essentially as described in Preparation 22.

HRMS: $m/z = 373.1749$ (M+H)

Preparation 111

1-iodo-2-oxo-2-(morpholin-4-yl)ethane

Dissolve 1-chloro-2-oxo-2-(morpholin-4-yl)ethane (7.0 g, 42.8 mmol) and sodium iodide (8.0 g, 53.4 mmol) in 2-butanone (150 mL) and reflux for 3 hours under nitrogen.

Dilute with ethyl acetate (200 mL), filter, concentrate under reduced pressure and chromatograph on flash silica using neat ethyl acetate to obtain 9.4 g (86%) of the title compound as a yellow oil.

HRMS: $m/z = 255.9837$ (M+H)

Preparation 112

2-(2,3-Dihydrobenzo[1,4]dioxin-5-yl)acetamide

5 (2,3-Dihydrobenzo[1,4]dioxin-5-yl)methanol

Dissolve 2,3-dihydroxybenzaldehyde (25 g, 181 mmol) and 1,2-dibromoethane (34 g, 181 mmol) in N,N-dimethylformamide (500 mL). Add cesium carbonate (118 g, 362 mmol), stir and reflux under nitrogen for 2 hours. Cool the reaction to 20°C, dilute with absolute ethanol (250 mL) and add sodium borohydride (6.8 g, 181 mmol). Stir at 20°C for 1 hour and concentrate under high vacuum to remove the ethanol and dimethylformamide. Dilute the residue with diethyl ether and wash with distilled water, 0.25 molar aqueous sodium hydroxide, and aqueous saturated sodium chloride. Dry the organic phase over anhydrous magnesium sulfate, filter and concentrate under reduced pressure. Chromatograph on flash silica using a gradient from 75% hexane, 25% ethyl acetate to 25% hexane, 75% ethyl acetate to obtain 8.1 g (27%) of the desired compound as a white solid.

HRMS: $m/z = 166.0621$ (M)

(2,3-Dihydrobenzo[1,4]dioxin-5-yl)-chloromethane

Dissolve (2,3-Dihydrobenzo[1,4]dioxin-5-yl)methanol (1.8 g, 10.8 mmol) in dichloromethane (15 mL). Add neat thionyl chloride (2 mL, 27.4 mmol) dropwise to the stirring reaction mixture at 25°C under nitrogen. Stir the reaction for 15 minutes and concentrate under reduced pressure to obtain 2.0 g (100%) of the desired compound as a yellow oil.

HRMS: $m/z = 184.0290$ (M)

(2,3-Dihydrobenzo[1,4]dioxin-5-yl)acetonitrile

Add (2,3-Dihydrobenzo[1,4]dioxin-5-yl)-chloromethane (1.9 g, 10.2 mmol) and sodium cyanide (655 mgs, 13.3 mmol) to dimethylsulfoxide (20 mL). Stir under nitrogen at 65°C for 18 hours. Dilute the reaction with ethyl acetate, wash with 0.1 molar aqueous sodium carbonate and aqueous saturated sodium chloride. Dry the organic phase over anhydrous magnesium sulfate, filter and concentrate under reduced pressure.

Chromatograph on flash silica using a gradient from neat hexane to 50% ethyl acetate in hexane to obtain 1.23 g (68%) of the desired compound as a white solid.

HRMS: $m/z = 175.0624$ (M)

5 Nitrile Hydrolysis

Beginning with (2,3-Dihydrobenzo[1,4]dioxin-5-yl)acetonitrile (1.1 g, 6.2 mmol), 850 mg (70%) of the title compound is prepared as a white solid essentially as described in Preparation 79.

HRMS: $m/z = 194.0810$ (M+H)

Preparation 113

5-Fluoro-1H-indole-7-carboxaldehyde

(5-Fluoro-2-nitrophenyl)methanol

Dissolve 5-fluoro-2-nitrobenzoic acid (15 g, 81.08 mmol) in anhydrous tetrahydrofuran (200 mL) and add dropwise with stirring at 20°C a 1 molar solution of borane in tetrahydrofuran (243 mL, 243 mmol). Stir the mixture at 20°C for 72 hours then add methanol (200 mL). Concentrate under reduced pressure and purify the residue by flash column chromatography (silica gel, 10-30% ethyl acetate/hexane) to obtain 13.92 g (100%) of the title compound as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.14(dd, 1H), 7.48(dd, 1H), 7.06(ddd, 1H), 4.98(s, 3H), 2.04 (s, 1H)

5-Fluoro-2-nitrobenzaldehyde

Dissolve (5-fluoro-2-nitrophenyl)methanol (13.92 g, 81.08 mmol) in dichloromethane (284 mL). Add 4Å molecular sieves (73 g) and pyridinium dichromate (36.58 g, 97.3 mmol). Stir the mixture at 20°C for 6 hours. Filter the crude reaction mixture through a short silica gel column. Remove the solvent under reduced pressure and purify the residue by flash chromatography (silica gel, 10-20% ethyl acetate/hexane) to obtain 9.43 g (69%) of title compound as colorless oil.

$^1\text{H-NMR}(\text{CDCl}_3)$: δ 10.44(d, 1H), 8.22(dd, 1H), 7.62(dd, 1H), 7.41(ddd, 1H)

2-Dibutoxymethyl-4-fluoro-1-nitrobenzene

Dissolve 5-fluoro-2-nitrobenzaldehyde (9.43 g, 55.81 mmol), 1-butanol (12.41 g, 167.4 mmol) and 4-toluenesulfonic acid monohydrate (0.9 g, 4.7 mmol) in toluene (84 mL). Heat the reaction mixture to reflux, and remove the water using a Dean-Stark apparatus. Continue to heat the reaction mixture for 3 hours. Add water and extract the aqueous layer with ethyl acetate. Combine the organic layers and dry over anhydrous sodium sulfate. Filter, concentrate under reduced pressure and purify by flash column chromatography (1% v/v triethylamine buffered silica gel, 5% ethyl acetate/hexane) to obtain 15.8 g (95%) of the title compound as colorless oil.

¹H-NMR(CDCl₃): δ 7.90(dd, 1H), 7.53(dd, 1H), 7.12(ddd, 1H), 6.04(s, 1H), 3.64(t, 1H), 3.62(t, 1H), 3.54(t, 1H), 3.52(t, 1H), 1.59(m, 4H), 1.38(s, 4H), 0.92(t, 6H).

Ring formation/deprotection

Dissolve 2-dibutoxymethyl-4-fluoro-1-nitrobenzene (15.8 g, 52.84 mmol) in tetrahydrofuran (528 mL) under nitrogen and cool the solution to -40°C. Add with stirring a 1 molar solution of vinylmagnesium bromide in tetrahydrofuran (211 mL, 211 mmol), maintaining a temperature of -40°C. Stir the reaction mixture at -40°C for 40 minutes, then add aqueous saturated ammonium chloride. Extract the aqueous layer with ethyl acetate. Combine the organic layers, dry over anhydrous sodium sulfate, filter, and concentrate under reduced pressure. Dissolve the residue in tetrahydrofuran (160 mL) and cool to 0°C. Add 0.5 N aqueous hydrochloric acid (20 mL) and stir the mixture at 0°C for 1 hour. Add aqueous saturated sodium hydrogen carbonate (200 mL) and extract the aqueous layer with ethyl acetate. Combine the organic layers, dry over anhydrous sodium sulfate, filter, concentrate under reduced pressure and purify by flash column chromatography (silica gel, 5% ethyl acetate/hexane) to obtain 4.76 g (55%) of the title compound as a white solid.

¹H-NMR(CDCl₃): δ 10.07(s, 2H), 7.62(dd, 1H), 7.40(m, 1H), 6.60(t, 1H)

Preparation 114

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)acetamide

Hydrogenate a mixture 2-(imidazo[1,2-a]pyridin-3-yl)acetamide (0.64 gm) and 0.158 gm platinum oxide in 200 mL ethanol saturated with hydrogen chloride at 60 p.s.i.

for 2 hours at room temperature. Filter the reaction mixture and concentrate the filtrate under reduced pressure to provide 0.58 gm ethyl 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)acetate. Heat a solution of this ester in 40 mL 2 M ammonia in methanol in a sealed tube at 100°C for 2 hours. Cool the reaction mixture to room temperature and concentrate under reduced pressure to a volume of about 5 mL. Dilute with ethyl acetate and filter the resulting solid to provide the title compound.

MS(ES): $m/z = 180.1 (M^+ + 1)$

Preparation 115

2-(pyrazolo[2,3-a]pyridin-3-yl)acetamide

Beginning with 2-(pyrazolo[2,3-a]pyridin-3-yl)acetonitrile, the title compound is prepared essentially as described in Preparation 79.

Preparation 116

2-(4-Chlorofuro[3,2-c]pyridin-7-yl)acetamide

7-(Hydroxymethyl)furo[3,2-c]pyran-4-one

Add lithium diisopropylamine (0.454 mole) as a solution in tetrahydrofuran (100) mL to a solution of 3-furoic acid (23.36 g, 0.208 mole) at -78 °C over 30 minutes and stir for 1 hour at -78 °C. To the resulting di-anion add 1,3-Bis-triisopropylsilanyloxy-propan-2-one as a solution in tetrahydrofuran (250 mL) over 30 minutes and stir at -78 °C for 1 hour and allow to warm to room temperature overnight. Quench the reaction with saturated aqueous ammonium chloride, pour into ethylacetate (1 L), add 1N HCL (1L) and separate the two layers. Wash the organic layer with 1N HCl, water, and brine, dry over magnesium sulfate, filter and concentrate to an oil. Dissolve the crude oil in 50% tetrahydrofuran and 50% 3N HCl (1L) and heat a reflux over night. Distill off tetrahydrofuran, concentrate under reduced pressure and, add acetonitrile remove it under reduced pressure to azeotrope off the remaining water. Dissolve the resulting crude oil in acetonitrile (250 mL) and add the solution to a solution of toluene containing a catalytic amount of p-toluenesulfonic acid at reflux that is fitted with a Dean Stark trap over 30 minutes. Toluene was added to replace the acetonitrile and water removed by distillation and azeotrope (500 mL). Heat the solution at reflux until it appears no further water is being removed. The hot solution was poured into an erlenmeyer flask and allowed to

cool. Triturate the brown remaining residue with ethylacetate and methanol and combine it with the toluene solution and concentrate. Dilute with ethylacetate and wash with saturated aqueous sodium bicarbonate and brine, dry over magnesium sulfate and concentrate to an off white solid. Purification by flash chromatography eluting with
5 hexane:ethylacetate gives 13.27 g (42%) of the title compound as a white solid.
MS(ES): $m/e = 167.0$ ($M^+ + 1$).

Methyl (4-oxo-4,5-dihydrofuro[3,2-c]pyridin-7-yl)acetate

Combine 7-(hydroxymethyl)furo[3,2-c]pyran-4-one (8.28 g, 49.8 mmol),
10 ammonium acetate (76.8 g, 996 mmol), and glacial acetic acid and heat at reflux for 3.5 hours. Cooling to room temperature, pouring into ethylacetate, washing with water saturated aqueous sodium bicarbonate, and brine, drying over magnesium sulfate, filtering and concentrating gives 4.42 g (42%) of the title compound.

$^1\text{H-NMR}(\text{DMSO-}d_6)$: δ 11.5(s, 1H), 7.91 (d, $J = 2$ Hz), 7.41(s, 1H), 6.94(d, $J = 1.6$ Hz,
15 1H), 5.06(s, 2H), 2.00(s, 3H).

(4-Oxo-4,5-dihydrofuro[3,2-c]pyridin-7-yl)acetonitrile

Combine methyl (4-oxo-4,5-dihydrofuro[3,2-c]pyridin-7-yl)acetate (4.42 g, 21.3 mmol), sodium cyanide (5.22 g, 106 mmol), and dimethylsulfoxide (44 mL) and heat at
20 80 °C for 1 hour. Cool to room temperature, pour into ethyl acetate, wash sequentially with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dry over magnesium sulfate, filter, and concentrate under reduced pressure to provide the desired compound (3.63 g, 63%).

MS(ES): $m/z = 173.1$ ($M - 1$)

Chlorination

Add phosphorus oxychloride (150 mL) to (4-oxo-4,5-dihydrofuro[3,2-c]pyridin-7-yl)acetonitrile (2.363 g, 13.5 mmol) and heat at reflux. Concentrate under reduced pressure, dissolve the residue in tert-butanol (35 mL), and heat to reflux. Add KOH
30 (85%) pellets and heat at reflux for 15 minutes. Cool the reaction and pour into ethyl acetate. Wash the organic solution with water and saturated aqueous sodium chloride, dry over sodium sulfate, and filter. Subject residue to flash chromatography, eluting with

ethyl acetate:methanol to provide the title compound (858 mg, 31%) as an off white solid.

MS(ES): $m/e = 210.9$ (M^+).

Preparation 117

5 2-(4-Dimethylaminofuro[3,2-c]pyridin-7-yl)acetamide

Combine 2-(4-chlorofuro[3,2-c]pyridin-7-yl)acetamide (850 mg, 4.21 mmol), dimethylformamide (5 mL) and ethanolamine (0.76 mL, 12.63 mmol). Heat the reaction at 130 °C overnight. Add additional ethanolamine (0.25 ml) and heat at 130 °C overnight. Cool to room temperature, concentrate, and dilute with ethyl acetate. Wash
10 with saturated aqueous sodium bicarbonate and concentrate. Subject to flash chromatography, eluting with ethyl acetate:methanol to provide the title compound as a white solid (400 mg, 43%).

MS(ES): $m/e = 220.1$ ($M^+ + 1$)

15 Preparation 118

2-(7-cyanoimidazo[1,2-a]pyridin-3-yl)acetamide

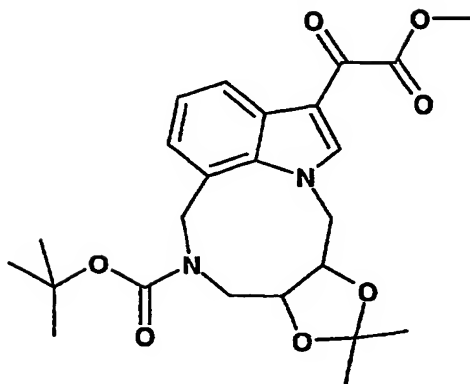
Add 100 mL ammonium hydroxide to a sealed tube containing 12.5 gm (90.21 mMol) 2-chloro-3-cyanopyridine. Seal the tube and heat the suspension at 120°C for 6 hours. Cool the reaction mixture to room temperature and partition between ethyl acetate
20 and saturated aqueous sodium bicarbonate. Extract the aqueous phase with ethyl acetate (3 x 100 mL) followed by 70:30 ethyl acetate:n-butanol (2 x 100 mL). Combine organic phases and concentrate under reduced pressure to provide 2-amino-3-cyanopyridine.

MS(ES): $m/e = 120$ ($M^+ + 1$)

2-amino-3-cyanopyridine is reacted as described in Preparation 99 to provide the
25 title compound.

MS(ES): $m/e = 230$ ($M^+ + 1$)

Preparation 119



Methyl (5,6-(2,2-dimethyl-[1,3]dioxolanyl)-8-(tert-butoxycarbonyl)-
[1,5]diazaperhydroonino[8,9,1-hi]indol-1-yl)oxoacetate

5 Oxidation

Add osmium tetroxide (9mg, 0.035 mmol) in butanol (1.5 mL) to a solution of the alkene prepared in Preparation 18 (0.5 g, 1.75 mmol) in 9:1 tetrahydrofuran:water. Stir the mixture for 1 hour at room temperature. Quench with NaHSO₃, dilute with ethyl acetate, and filter. Wash the organic layer sequentially with water and saturated aqueous sodium chloride, dry over sodium sulfate and concentrate under reduced pressure. Subject to silica gel chromatography, eluting with a gradient of 3:1-0:1 hexane:ethyl acetate to provide the desired diol.

Diol Protection

Dissolve the diol (0.22 g, 0.66 mmol) and p-toluenesulfonic acid (25 mg) in 5 mL acetone and stir the mixture for 1 hour at room temperature. Concentrate under reduced pressure and subject the residue to silica gel chromatography, eluting with a gradient of hexane containing from 0-33% ethyl acetate to provide the protected diol (150 mg, 61%).

Oxoacetic acid ester formation

Beginning with the protected diol, the title compound is prepared as a yellow solid essentially as described in Preparation 22 (60 mg).

MS(ES): $m/z = 459 (M^+ + H)$

Preparation 120

3-(8-tert-butoxycarbonyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole

Add potassium tert-butoxide (2.19 ml, 2.19 mmol, 1M solution in tetrahydrofuran) to a suspension of 2-(benzofur-7-yl)acetamide (0.13 g, 0.73 mmol) and (8-tert-butoxycarbonyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)oxoacetic acid methyl ester (0.283 g, 0.73 mmol) in dimethylformamide (5 ml). Stir the reaction for 2 hours, quench with 1N HCl, and extract into ethyl acetate. Wash the organic extracts sequentially with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dry over magnesium sulfate, filter, and concentrate under reduced pressure. Chromatograph on flash silica, eluting with a gradient from neat hexane to 100% ethyl acetate to obtain the title compound as an orange solid (0.19 g, 51%).

MS(ES): $m/z = 512.1 (M^+ + 1)$

The compounds of Preparations 121-125 are prepared essentially as described in

Preparation 120.

Prep.	Compound	Data
121	3-(8- <u>tert</u> -butoxycarbonyl-[1,5]diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(5-Fluoro-4-methoxybenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 560.8 (M^+ + 1)$
122	3-(8- <u>tert</u> -butoxycarbonyl-[1,5]diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 513.2 (M^+ + 1)$
123	3-(6- <u>tert</u> -butoxycarbonyl-[1,8]diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 513.2 (M^+ + 1)$
124	3-(6- <u>tert</u> -butoxycarbonyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole	HRMS: $m/z = 485.1832$
125	3-(6- <u>tert</u> -butoxycarbonyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(isoquinolin-5-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 495.1 (M^+ + 1)$

The compounds of Examples 1-56 are prepared essentially as described in

Preparation 120.

1	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(1-methyl-1H-indol-4-yl)-2,5-dioxo-2,5-dihydropyrrole hydrochloride	MS(ES): $m/z = 431.0 (M - 1)$
---	---	-------------------------------

2	3-(6-(<u>tert</u> -butoxycarbonyl)-5,6-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-(4-(1-(3-hydroxyprop-1-yl)-1H-indol-4-yl)-2,5-dioxopyrrole	MS(ES): m/z = 541.3 (M ⁺ +1)
3	3-(5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(1-(3-hydroxyprop-1-yl)-1H-indol-4-yl)-2,5-dioxopyrrole	MS(ES): m/z = 426.1 (M ⁺ +1)
4	3-(8- <u>tert</u> -butoxycarbonyl-[1,5]diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 512.2 (M ⁺ +1)
5	3-(6-(<u>tert</u> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(4-methoxybenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 514.1
6	3-(5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 369.1 (M ⁺ +1)
7	3-(6-methanesulfonyl-5,6-dihydro-[1,4]diazepino-[6,7,1-hi]indol-7-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 462.09 (M ⁺ +1)
8	3-(6-(<u>tert</u> -butoxycarbonyl)-5,6-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-(4-(5-methoxybenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 514.1 (M ⁺ +1)
9	3-(8- <u>tert</u> -butoxycarbonyl-[1,5]diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(5-methoxybenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 542.1 (M ⁺ +1)
10	3-(8- <u>tert</u> -butoxycarbonyl-[1,5]diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(4-methoxybenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 542.1 (M ⁺ +1)
11	3-(6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(5-fluorobenzofur-4-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 401.9 (M ⁺ +1)
12	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(isoquinolin-5-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 401.9 (M ⁺ +1)
13	3-(8- <u>tert</u> -butoxycarbonyl-[1,5]diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(benzofur-4-yl)-2,5-dioxopyrrole	MS(ES): m/z = 512.1 (M ⁺ +1)
14	3-(6-(<u>tert</u> -butoxycarbonyl)-5,6-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-(4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 502.1 (M ⁺ +1)
15	3-(8- <u>tert</u> -butoxycarbonyl-[1,5]diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 528.7 (M ⁻ -1)
16	3-(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 369.2 (M ⁺ +1)
17	3-(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)-4-(imidazo[1,2-a]pyridin-5-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 369.1 (M ⁺ +1)
18	3-(5-oxo-6-propyl-5,6-dihydro-[1,4]diazepino[6,7,1-hi]indol-7-yl) 3-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 440.2 (M ⁺ +1)

19	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(5-fluoro-4-methoxybenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 460 (M ⁺ +1)
20	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(4,5-difluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 448.2 (M ⁺ +1)
21	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(4-fluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 430.2 (M ⁺ +1)
22	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(5,6-difluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 448.2 (M ⁺ +1)
23	3-(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)-4-(6-fluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 402.1 (M ⁺ +1)
24	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(6-fluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 430.2 (M ⁺ +1)
25	3-(6-(<u>tert</u> -butoxycarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(Furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 499.2 (M ⁺ +1)
26	3-(4,5,6,7-tetrahydroazepino[3,2,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 384.1 (M ⁺ +1)
27	3-(6-(<u>tert</u> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-4-yl)-2,5-dioxopyrrole	HRMS: 484.1856 (M+H)
28	3-(6-(<u>tert</u> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-5-yl)-2,5-dioxopyrrole	HRMS: 488.1813 (M+H)
29	3-(6-(<u>tert</u> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzo-[1,4]dioxin-6-yl)-2,5-dioxopyrrole	HRMS: 502.1960 (M+H)
30	3-(6-(<u>tert</u> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzothien-4-yl)-2,5-dioxopyrrole	HRMS: 500.1634 (M+H)
31	3-(6-(<u>tert</u> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 486.2051 (M+H)
32	3-(6-(<u>tert</u> -butoxycarbonyl)-5,6-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-4-yl)-2,5-dioxopyrrole	MS(ES): m/z = 486.1 (M ⁺ +1)
33	3-(8- <u>tert</u> -butoxycarbonyl)-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 538.1940 (M+Na)
34	3-(8- <u>tert</u> -butoxycarbonyl)-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 514.2341 (M+H)

35	3-(9-methyl-6-(<i>tert</i> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 496.3$ ($M^+ - 1$)
36	3-(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(4-methoxybenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 399.1355 ($M + H$)
37	3-(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(5-methoxybenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 399.1347 ($M + H$)
38	3-(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-((3-hydroxypropoxy)benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 443.2$ ($M^+ + 1$)
39	3-(6-(<i>tert</i> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(6-methoxybenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 514.2$ ($M^+ + 1$)
40	3-(6-(<i>tert</i> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,2-difluorobenzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 373.6$ ($M^+ + 1$)
41	3-(6-(<i>tert</i> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(thieno[3,2-b]pyridin-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 501.2$ ($M^+ + 1$)
42	3-(8- <i>tert</i> -butoxycarbonyl)-[1,5]diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(thieno[3,2-b]pyridin-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 529.2$ ($M^+ + 1$)
43	3-(4,5,6,7-tetrahydroazepino[3,2,1-hi]indol-1-yl)-4-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 401.1$ ($M^+ + 1$)
44	3-(4,5,6,7-tetrahydroazepino[3,2,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-5-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 387.2$ ($M^+ + 1$)
45	3-(4,5,6,7-tetrahydroazepino[3,2,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 387.2$ ($M^+ + 1$)
46	3-(4,5,6,7-tetrahydroazepino[3,2,1-hi]indol-1-yl)-4-(benzofur-4-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 383.1$ ($M^+ + 1$)
47	3-(4,5,6,7-tetrahydroazepino[3,2,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 383.1$ ($M^+ + 1$)
48	3-(4,5,6,7-tetrahydroazepino[3,2,1-hi]indol-1-yl)-4-(1,3-dihydroisobenzofur-5-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 385.1$ ($M^+ + 1$)
49	3-(6-(<i>tert</i> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(1,3-dihydroisobenzofur-5-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 431$ ($M^+ + 1$ - (t-Bu))
50	3-(6-(<i>tert</i> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzimidazol-4-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 482.1$ ($M^+ + 1$)
51	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(pyrazolo[2,3-a]pyridin-3-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): $m/z = 384.2$ ($M^+ + 1$)
52	3-(6-(<i>tert</i> -butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzo[1,4]dioxin-5-yl)-2,5-dioxopyrrole	HRMS: $m/z = 502.1983$ ($M + H$)
53	3-(6-(<i>tert</i> -butoxycarbonyl)-9-fluoro-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-	MS(ES): $m/z = 502.2$ ($M^+ + 1$)

	2,5-dioxopyrrole	
54	3-(6-(tert -butoxycarbonyl)-7-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo-[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: m/z = 502.1983 (M+H)
55	3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(4-(dimethylamino)furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 442.2 (M ⁺ +1)
56	3-(7-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 399.1 (M ⁺ +1)

EXAMPLE 57

3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole dihydrochloride

5 Add ethanethiol (1.0 g, 31.2 mmol) to a flask containing 3-(8-~~tert~~-butoxycarbonyl-[1,5]diazoperhydroonino[8,9,1-hi]-indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole (0.95 g, 1.86 mmol). Add 4N HCl in dioxane (10 ml, 40 mmol) to the flask and stir for 12 hours. Filter the resulting solid and wash with an appropriate solvent (appropriate solvents include ethyl acetate, diethyl ether, and dioxane). Dry the solid
10 under high vacuum at 45°C to give the title compound as a bright orange solid (0.83 g, 92%).

MS(ES): m/z = 412.2(M⁺+1)

The hydrochloride salt may be converted to the free base by dissolving the salt in methanol, passing the solution through a Varian® BondElut™ SCX column, eluting the
15 column with 2 molar ammonia in methanol and concentrating under reduced pressure.

The compounds of EXAMPLES 58-116 are prepared essentially as described in EXAMPLE 57.

Example	Compound	Data
58	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(1-(3-hydroxyprop-1-yl)-1H-indol-4-yl)-2,5-dioxopyrrole	¹ H-NMR*
59	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 412.1 (M ⁺ +1)
60	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-((4-methoxybenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 414.2 (M ⁺ +1)
61	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 383.9 (M ⁺ +1)

62	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(5-methoxybenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 413.9 (M ⁺ +1)
63	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(5-methoxybenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 442.0 (M ⁺ +1)
64	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(4-methoxybenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 442.0 (M ⁺ +1)
65	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-4-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 412.1 (M ⁺ +1)
66	3-(6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(4-fluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 402.1 (M ⁺ +1)
67	3-(6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(4,5-difluorobenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 420.1 (M ⁺ +1)
68	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(1-(3-hydroxypropyl)-1H-indol-4-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 469.3 (M ⁺ +1)
69	3-(6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(4-fluoro-5-methoxybenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 432.2 (M ⁺ +1)
70	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 430.2 (M ⁺ +1)
71	3-(6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 384.2 (M ⁺ +1)
72	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(1-methyl-1H-indol-4-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 425.3 (M ⁺ +1)
73	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(5,6-difluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 420.2 (M ⁺ +1)
74	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(3-furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 385.1 (M ⁺ +1)
75	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 413.2 (M ⁺ +1)
76	3-([1,7]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 413.2 (M ⁺ +1)
77	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: 384.1348 (M+H)
78	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-4-yl)-2,5-dioxopyrrole	HRMS: 384.1344 (M+H)
79	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-5-yl)-2,5-dioxopyrrole	HRMS: 388.1294 (M+H)
80	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-2,5-dioxopyrrole	HRMS: 402.1447

	4-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-2,5-dioxopyrrole	(M+H)
81	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzothien-7-yl)-2,5-dioxopyrrole	HRMS: 400.1118 (M+H)
82	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 388.1298 (M+H)
83	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzothien-4-yl)-2,5-dioxopyrrole	HRMS: 400.1142 (M+H)
84	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 386.1497 (M+H)
85	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-4-yl)-2,5-dioxopyrrole	HRMS: 386.1519 (M+H)
86	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 416.1602 (M+H)
87	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 414.1823 (M+H)
88	3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: 398.1500 (M+H)
89	3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 402.1454 (M+H)
90	3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 416.1408 (M+H)
91	3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 400.1675 (M+H)
92	3-(9-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 398.3 (M ⁺ +1)
93	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(4-(3-(diethylamino)propoxy)benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 513.3 (M ⁺ +1)
94	3-([1,7]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 412.2 (M ⁺ +1)
95	3-([1,7]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(5,6-difluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	HRMS: m/z = 448.1493
96	3-([1,7]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	HRMS: m/z = 430.1582
97	3-([1,7]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(6-fluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 430.2
98	3-(6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(isoquinolin-5-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 395.2 (M ⁺ +1)
99	3-([1,7]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 412.2 (M ⁺ +1)

100	3-([1,6]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 412.2 (M ⁺ +1)
101	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,2-difluorobenzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	MS(ES): m/z = 424.1 (M ⁺ +1)
102	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(thieno[3,2-b]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 429.1 (M ⁺ +1)
103	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(1,3-dihydroisobenzofur-5-yl)-2,5-dioxopyrrole	MS(ES): m/z = 386.7 (M ⁺ +1)
104	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzimidazol-4-yl)-2,5-dioxopyrrole	MS(ES): m/z = 384.0 (M ⁺ +1)
105	3-(5-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 398.2 (M ⁺ +1)
106	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 388.2 (M ⁺ +1)
107	3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 398.2 (M ⁺ +1)
108	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzo[1,4]dioxin-5-yl)-2,5-dioxopyrrole hydrochloride	HRMS: m/z = 402.1438 (M ⁺ +H)
109	3-(9-fluoro-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 402.1 (M ⁺ +1)
110	3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 510.2 (M ⁺ +1)
111	3-(7-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: m/z = 402.1460 (M ⁺ +H)
112	3-(7-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	HRMS: m/z = 398.1605 (M ⁺ +H)
113	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(thieno[3,2-b]pyridin-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 429.1 (M ⁺ +1)
114	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 402.2 (M ⁺ +1)
115	3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 399.1 (M ⁺ +1)
116	3-(7-((piperidin-4-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 496.2 (M ⁺ +1)

*¹H-NMR(DMSO-d₆): δ 11.05(bs, 1H), 7.93(s, 1H), 7.5(d, J = 8Hz, 1H), 7.1-7.18(m, 2H), 7.04(d, J = 7 Hz, 1H), 6.8 (d, J = 7Hz, 1H), 6.3 (dd, J = 7, <1 Hz, 1H), 6.0 (m, 2H), 4.5 (t, J = 1 Hz, 1H), 4.27 (m, 2H), 4.17 (t, J = 7 Hz, 2H), 4.05 (m, 2H), 3.25 (m, 2H), 3.18 (m, 2H), 1.78(m, 2H)

5

EXAMPLE 117

3-(5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinazolin-1-yl)-4-(isoquinolin-5-yl)-2,5-dioxo-2,5-dihydro-1H-indole

Add trifluoroacetic acid (250μL) to 3-(5-(tert-butoxycarbonyl)-5,6-dihydro-1H-pyrrolo-[3,2,1-ij]quinazolin-1-yl)-4-(isoquinolin-5-yl)-2,5-dioxo-2,5-dihydro-1H-indole (0.400 g, 0.830 mmol) in dichloromethane (5 mL) and stir the reaction mixture at room temperature for 4 hours. Dilute the reaction with 300 mL dichloromethane and carefully quench with saturated sodium bicarbonate solution (200 mL). Separate the phases and wash the organic phase sequentially with water (1 x 75 mL) and saturated aqueous sodium chloride (1 x 75 mL), dry over anhydrous magnesium sulfate, and concentrate under reduced pressure to provide the title compound.

MS(ES): m/z = 383.1(M⁺+1)

EXAMPLE 118

3-(5,6-dihydroxy-[1,5]diazaperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole

Beginning with methyl (5,6-(2,2-dimethyl-[1,3]dioxolanyl)-8-(tert-butoxycarbonyl)-[1,5]diazaperhydroonino[8,9,1-hi]indol-1-yl)oxoacetate and 2-(benzofur-7-yl)acetamide, 3-(5,6-(2,2-dimethyl-[1,3]dioxolanyl)-8-(tert-butoxy-carbonyl)-[1,5]diazaperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole is prepared essentially as described in Preparation 120. This material is treated with trifluoroacetic acid as described in EXAMPLE 117 to provide the title compound.

MS(ES): m/z = 444 (M⁺+H)

EXAMPLE 119

3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(indol-7-yl)-2,5-dioxopyrrole

Add aluminum chloride (0.014 g, 0.1 mmol) to a flask containing 3-(6-(tert-butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(indol-7-yl)-2,5-

dioxopyrrole (0.05, 0.1 mmol) in methylene chloride (25 ml). Quench the reaction with saturated aqueous sodium bicarbonate, extract into ethyl acetate, wash combined organic layers with saturated aqueous sodium chloride, dry over magnesium sulfate, and concentrate under reduced pressure. Chromatograph on flash silica using a gradient from neat ethyl acetate to 10% methanol: ethyl acetate to obtain the title compound as an orange solid (10 mg, 26%).

MS(ES): $m/z = 383.0$ ($M^+ + 1$)

EXAMPLE 120

10 3-(6-methyl-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]-indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole

Add 3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole (140 mg, 0.35 mmol), paraformaldehyde (264 mg, 8.8 mmol), potassium acetate (104 mg, 1.0 mmol), sodium cyanoborohydride (220 mg, 3.5 mmol), and glacial acetic acid (1.5 mL) to 2-methoxyethanol (13.5 mL). Stir and slowly heat to reflux under nitrogen. After 30 minutes dilute with 1:1 diethyl ether:ethyl acetate. Wash sequentially with aqueous 0.5 molar sodium hydrogen carbonate and distilled water, and pass the organic phase through a Varian® BondElut™ SCX column. Rinse the column with absolute methanol. Elute with 2M ammonia in methanol, concentrate under reduced pressure, filter, rinse the solid with cold methanol and dry under reduced pressure to provide the title compound as an orange solid (115 mg, 79%).

HRMS: 412.1663 ($M+H$).

The compounds of EXAMPLES 121-145 are prepared essentially as described in

25 EXAMPLE 120.

Example	Compound	Data
121	3-(6-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 398.1$ ($M^+ + 1$)
122	3-(8-methyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 426.2$ ($M^+ + 1$)
123	3-(8-methyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): $m/z = 426.2$ ($M^+ + 1$)

124	3-(6-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]-indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 398.2 (M ⁺ +1)
125	3-(6-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]-indol-1-yl)-4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 416.1 (M ⁺ +1)
126	3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-7-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 444.6 (M ⁺ +1)
127	3-(6-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]-indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 399.1 (M ⁺ +1)
128	3-(6-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzothien-7-yl)-2,5-dioxopyrrole	HRMS: 414.1300 (M+H)
129	3-(6-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]-indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 402.1461 (M+H)
130	3-(6-isopropyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 444.6 (M ⁺ +1)
131	3-(6-cyclohexyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 484.2 (M ⁺ +1)
132	3-(6-(tetrahydropyran-4-yl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 468.2 (M ⁺ +1)
133	3-(6-(α-methylbenzyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 488.2 (M ⁺ +1)
134	3-(6-((imidazol-2-yl)methyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 464.2 (M ⁺ +1)
135	3-(6-(isopropyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 440.2 (M ⁺ +1)
136	3-(6-(isopropyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benz[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: m/z = 430.1781 (M ⁺ +H)
137	3-(6-(isopropyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: m/z = 428.1986 (M ⁺ +H)
138	3-(6-(methyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzo[1,4]dioxin-5-yl)-2,5-dioxopyrrole	HRMS: m/z = 416.1610 (M ⁺ +H)
139	3-(6-(isopropyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	HRMS: m/z = 440.1970 (M ⁺ +H)

140	3-(6-(tetrahydropyran-4-yl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	HRMS: m/z = 482.2046 ($M^+ + H$)
141	3-(6-(α -methylbenzyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	HRMS: m/z = 502.2138 ($M^+ + H$)
142	3-(6-(methyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: m/z = 416.1595 ($M^+ + H$)
143	3-(6-(ethyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: m/z = 416.1600 ($M^+ + H$)
144	3-(6-(methyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 413.1 ($M^+ + 1$)
145	3-(6-(isopropyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 441.2 ($M^+ + 1$)

EXAMPLE 146

3-(5-methyl-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinazolin-1-yl)-4-(isoquinolin-5-yl)-2,5-dioxopyrrole

- 5 Add a solution of 3-(5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinazolin-1-yl)-4-(isoquinolin-5-yl)-2,5-dioxopyrrole (0.300g, 0.7853 mmol) in anhydrous dimethylformamide (1.5 mL) to formalin (37% solution in water, 0.750 ml) in 2 ml glacial acetic acid and stir at 65°C for 2 hours. Pour into ice water and neutralize with 5.0N sodium hydroxide. Extract with 200 mL ethyl acetate, wash sequentially with
- 10 water (1 x 75 mL), and saturated aqueous sodium chloride (1 x 75 mL), dry over anhydrous magnesium sulfate, and concentration under reduced pressure. Dissolve the residue in 150 ml 2.0 M ammonia in methanol stir at room temperature for 2 hours, concentrate and purify by column chromatography to give the title compound as an orange solid.
- 15 MS(ES): m/z = 395.2($M^+ + 1$)

EXAMPLE 147

3-(6-formyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-
2,5-dioxopyrrole

Add 3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-
2,5-dioxopyrrole (312 mg, 0.74 mmol) and sodium formate (130 mg, 1.91 mmol) to
formamide (12 mL) and stir under nitrogen at 140°C for 30 minutes. Dilute with ethyl
acetate:diethyl ether (1:1), wash sequentially with aqueous 0.25 M hydrochloric acid,
aqueous 0.5 M sodium hydrogen carbonate, and aqueous saturated sodium chloride,
dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure.
Recrystallize the residue from methanol and dry under reduced pressure to provide the
title compound as an orange solid (285 mg, 93%).

HRMS: 412.1324 (M+1)

EXAMPLE 148

3-(6-(phenoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-
(benzofur-7-yl)-2,5-dioxopyrrole

Cool a solution of 0.17 gm (0.44 mMol) 3-(6,7-dihydro-6H-[1,4]diazepino-
[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole in 5 mL methanol containing
0.12 mL (0.88 mMol) triethylamine. Add 0.10 gm (0.66 mMol) phenyl
chloroformate. Stir the reaction mixture for 3 hours. Quench the reaction with water
and extract with ethyl acetate. Subject the organic phase to flash silica gel
chromatography, eluting with a gradient of hexane containing from 50% to 0% ethyl
acetate. Combine fractions containing desired product and concentrate them under
reduced pressure to provide 0.096 gm of the title compound.

MS(ES): m/z = 504.2 (M⁺+1)

The compounds of EXAMPLES 149-230 are prepared essentially as described in
EXAMPLE 148.

Example	Compound	Data
149	3-(6-(3-trifluoromethylphenoxy carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 572 (M ⁺ +1)
150	3-(6-(4-methoxyphenoxy carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 534 (M ⁺ +1)

151	3-(6-(phenoxycarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: m/z = 518.1737 ($M^+ + H$)
152	3-(6-(methoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: m/z = 446.1352 ($M^+ + H$)
153	3-(6-(ethoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 456.2 ($M^+ + 1$)
154	3-(6-(isopropoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 470 ($M^+ + 1$)
155	3-(8-(isopropoxycarbonyl)-[1,5]diazaperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 444 ($M^+ + 1$)
156	3-(6-(butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 484 ($M^+ + 1$)
157	3-(6-(2-(methoxy)ethoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 486.2 ($M^+ + 1$)
158	3-(6-(2-(morpholin-4-yl)ethoxycarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: m/z = 555.2245 ($M + H$)
159	3-(6-((1-methylpiperazin-4-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: m/z = 514.2090 ($M + H$)
160	3-(6-((morpholin-4-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 497.2 ($M^+ + 1$)
161	3-(6-((morpholin-4-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 497.2 ($M^+ + 1$)
162	3-(6-((morpholin-4-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(7-cyanoimidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 522.1 ($M^+ + 1$)
163	3-(6-((morpholin-4-yl)carbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: m/z = 511.1978 ($M + H$)
164	3-(6-((pyrrolidin-1-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 497.2 ($M^+ + 1$)
165	3-(6-((piperidin-1-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 497.2 ($M^+ + 1$)

166	3-(6-(trimethylacetyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 468.2 (M ⁺ +1)
167	3-(6-(N,N-[dimethyl]aminocarbonyl)-[1,7]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 483.2 (M ⁺ +1)
168	3-(7-(N,N-[dimethyl]aminocarbonyl)-[1,6]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 483.2 (M ⁺ +1)
169	3-(8-(N,N-[dimethyl]aminocarbonyl)-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 483.2 (M ⁺ +1)
170	3-(8-(N,N-[dimethyl]aminocarbonyl)-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 487.1973 (M+H)
171	3-(6-(N,N-[dimethyl]aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 455.2 (M ⁺ +1)
172	3-(6-(N,N-[dimethyl]aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 473.2 (M ⁺ +1)
173	3-(6-(N,N-[dimethyl]aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 455.2 (M ⁺ +1)
174	3-(6-(N,N-[dimethyl]aminocarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 469.6 (M ⁺ +1)
175	3-(6-(N,N-[dimethyl]aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzo[1,4]dioxin-5-yl)-2,5-dioxopyrrole	HRMS: m/z = 473.1822 (M ⁺ +H)
176	3-(6-(N,N-[dimethyl]aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: m/z = 459.1690 (M ⁺ +H)
177	3-(6-(N,N-[dimethyl]aminocarbonyl)-[1,7]diazaperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 483.2 (M ⁺ +1)
178	3-(7-(N,N-[dimethyl]aminocarbonyl)-[1,6]diazaperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 483.2 (M ⁺ +1)
179	3-(6-(N,N-[dimethyl]aminocarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: m/z = 469.1889 (M ⁺ +H)
180	3-(6-(N,N-[dimethyl]aminocarbonyl)-7-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	

181	3-(6-(N,N-[dimethyl]aminocarbonyl)-7-methyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole hydrochloride	HRMS: m/z = 469.2000 ($M^+ + H$)
182	3-(6-(N,N-[dimethyl]aminocarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: m/z = 473.1841 ($M^+ + H$)
183	3-(8-propionyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: m/z = 470.2086 ($M + H$)
184	3-(6-propionyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 440.2 ($M^+ + 1$)
185	3-(6-acetyl-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 441.1 ($M^+ + 1$)
186	3-(8-propionyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 468.2 ($M^+ + 1$)
187	3-(6-propionyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 440.1 ($M^+ + 1$)
188	3-(8-acetyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 454.2 ($M^+ + 1$)
189	3-(8-propionyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 468.2 ($M^+ + 1$)
190	3-(6-acetyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 426.2 ($M^+ + 1$)
191	3-(8-acetyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 454.2 ($M^+ + 1$)
192	3-(6-acetyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(5-fluorobenzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 444.1 ($M^+ + 1$)
193	3-(6-butyryl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 454.2 ($M^+ + 1$)
194	3-(6-isobutyryl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 454.2 ($M^+ + 1$)
195	3-(8-propionyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-3-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 469.2 ($M^+ + 1$)
196	3-(8-acetyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-3-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 455.1 ($M^+ + 1$)

197	3-(6-propionyl-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 455.2 (M ⁺ +1)
198	3-(6-propionyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 441.2 (M ⁺ +1)
199	3-(6-acetyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 427.1 (M ⁺ +1)
200	3-(6-acetyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 430.1422 (M+H)
201	3-(6-acetyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[b]thien-7-yl)-2,5-dioxopyrrole	HRMS: 442.1251 (M+H)
202	3-(6-propionyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 444.1552 (M+H)
203	3-(6-acetyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 428.1599 (M+H)
204	3-(6-propionyl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 442.1796 (M+H)
205	3-(6-butyryl-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 456.1911 (M+H)
206	3-(8-acetyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 456.1921 (M+H)
207	3-(8-propionyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 472.1864 (M+H)
208	3-(6-isobutyryl-[1,7]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 480.3 (M+1)
209	3-(6-acetyl-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 441.1 (M ⁺ +1)
210	3-(8-propionyl-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: m/z = 469.1885 (M+H)
211	3-(6-propionyl-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 454.2 (M ⁺ +1)
212	3-(6-(N,N-dimethylaminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 456.2 (M ⁺ +1)

213	3-(6-((morpholin-4-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 498.1 (M ⁺ +1)
214	3-(6-((4-methylpiperazin-1-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 511.2 (M ⁺ +1)
215	3-(6-((pyrrolidin-1-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 482.2 (M ⁺ +1)
216	3-(6-((pyrrolidin-1-yl)carbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 399.1 (M ⁺ +1)
217	3-(6-((morpholin-4-yl)carbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 512.2 (M ⁺ +1)
218	3-(6-((4-methylpiperazin-1-yl)carbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 525.2 (M ⁺ +1)
219	3-(6-((methoxy)carbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 457.1 (M ⁺ +1)
220	3-(6-((ethoxy)carbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 471.1 (M ⁺ +1)
221	3-(6-((N,N-dimethylamino)carbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 470.2 (M ⁺ +1)
222	3-(6-((piperidin-1-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 496.2 (M ⁺ +1)
223	3-(6-((piperidin-1-yl)carbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 510.2 (M ⁺ +1)
224	3-(6-(octanoyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 511.2 (M ⁺ +1)
225	3-(6-(octanoyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 525.2 (M ⁺ +1)
226	3-(7-methyl-6-((morpholin-4-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride	MS(ES): m/z = 512.2 (M ⁺ +1)
227	3-(6-(isobutyryl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(4-(dimethylamino)furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 512.2 (M ⁺ +1)

228	3-(6-((N,N-dimethylamino)carbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(4-(dimethylamino)furo-[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 513.2 (M ⁺ +1)
229	3-(6-((ethoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 456 (M ⁺ +1)
230	3-(6-((isopropoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 470 (M ⁺ +1)

EXAMPLE 231

3-(6-glycyl-[1,7]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole trifluoroacetate

Combine 3-([1,7]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole (90 mg, 0.22 mmol), N-[tert-butoxycarbonyl]glycine (40 mg, 0.22 mmol), 4-N,N-dimethylaminopyridine (10 mg), triethylamine (0.091 ml, 0.66 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (63 mg, 0.33 mmol) in dichloromethane (5 ml) and stir at room temperature overnight. Load the reaction mixture directly onto a 10 gram SCX[™] Varian column, wash sequentially with methanol and 2.0 M ammonia in methanol. Combine fractions and concentrate under reduced pressure. Slurry the residue in dichloromethane (5 ml), add trifluoroacetic acid (1 ml), and stir for 1 hour. Concentrate under reduced pressure, treat the residue with diethyl ether, and filter the suspension to provide the title compound as a yellow solid.

HRMS: 469.1891.

The compounds of EXAMPLES 232- are prepared essentially as described in EXAMPLE 231.

Example	Compound	Data
232	3-(6-(propionyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 454.5 (M ⁺ +1)
233	3-(6-(butyryl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 468.6 (M ⁺ +1)
234	3-(6-(isobutyryl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 468.6 (M ⁺ +1)

235	3-(6-(isobutyryl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 469.2 (M ⁺ +1)
236	3-(6-(methoxyethoxyacetyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 514.2 (M ⁺ +1)
237	3-(6-(methoxyethoxyacetyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	MS(ES): m/z = 518.2 (M ⁺ +1)
238	3-(6-((1-(tert-butoxycarbonyl)piperidin-4-yl)carbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 610.2 (M ⁺ +1)
239	3-(6-(pyrazin-2-ylcarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: m/z = 504.1678 (M ⁺ +H)
240	3-(6-(propionyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzo[1,4]dioxin-4-yl)-2,5-dioxopyrrole	HRMS: m/z = 458.1729 (M ⁺ +H)
241	3-(6-(methoxyethoxyacetyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 500 (M ⁺ +1)
242	3-(6-(N,N-dimethylglycyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 469 (M ⁺ +1)
243	3-(6-((pyridin-3-yl)carbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 489 (M ⁺ +1)
244	3-(6-(pyrazin-2-ylcarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 490.2 (M ⁺ +1)
245	3-(8-(isobutyryl)-[1,5]diazoperhydroonino[8,9,1-hi]-indol-1-yl)-4-(benzo[1,3]dioxol-5-yl)-2,5-dioxopyrrole	HRMS: m/z = 486.2029 (M ⁺ +H)
246	3-(8-(N,N-dimethylglycyl)-[1,5]diazoperhydroonino[8,9,1-hi]-indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 497 (M ⁺ +1)
247	3-(8-((pyrazin-2-yl)carbonyl)-[1,5]diazoperhydroonino[8,9,1-hi]-indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 518 (M ⁺ +1)
248	3-(6-(oxoacetyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 456.2 (M ⁺ +1)

EXAMPLE 249

3-(6-(aminosulfonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole

Add 3-(6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride (300 mg, 0.714 mmol) and sulfamide (1.0 g, 10.4 mmol) to pyridine (20 mL). Reflux and stir under nitrogen for 20 minutes, concentrate under reduced pressure. Dilute the residue with ethyl acetate, wash sequentially with 0.25 M hydrochloric acid and aqueous saturated sodium chloride. Dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Precipitate the residue from ethyl acetate to obtain the title compound as an orange solid (125 mg, 37%).

MS(ES): $m/z = 463.1 (M+1)$.

The compounds of EXAMPLES 250-252 are prepared essentially as described in EXAMPLE 249.

Example	Compound	Data
250	3-(6-(aminosulfonyl)-5,6,7,8-tetrahydro-6H-[1,4]-diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): $m/z = 478.1 (M^++1)$
251	3-(6-(aminosulfonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): $m/z = 464.0 (M^++1)$
252	3-(6-(aminosulfonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(5-fluorobenofur-7-yl)-2,5-dioxopyrrole	MS(ES): $m/z = 481.0 (M^++1)$

EXAMPLE 253

3-(6-(N-[methyl]aminocarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride

Add 1,3-dimethylurea (3g) to 3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole dihydrochloride (50 mg, 0.1 mmol) and heat at 140°C for 20 minutes. Remove for heat and dilute with water (10 mL) and 1 N HCl (2 mL). Subject residue to reverse phase high performance chromatography and freeze dry fractions to provide the title compound as an orange solid (31 mg, 63%).
MS(ES): $m/z = 455.48 (M^++1)$

The compounds of EXAMPLES 254-263 are prepared essentially as described in EXAMPLE 253.

Example	Compound	Data
254	3-(8-(N-[methyl]aminocarbonyl)-[1,5]-diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(furo-[3,2-c]pyridin-3-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 470.2 (M ⁺ +1)
255	3-(6-(aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: 427.1405 (M+H)
256	3-(6-(N-[methyl]aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]-dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 445.1523 (M+H)
257	3-(8-(aminocarbonyl)-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 457.1903 (M+H)
258	3-(6-(aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(2,3-dihydrobenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 429.1563 (M+H)
259	3-(6-(aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzo[1,3]dioxol-4-yl)-2,5-dioxopyrrole	HRMS: 431.1346 (M+H)
260	3-(6-(N-[methyl]aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(furo[3,2-c]pyridin-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 399.1 (M ⁺ +1)
261	3-(6-(N-[methyl]aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 441.1 (M ⁺ +1)
262	3-(6-(N-[methyl]aminocarbonyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 498.3 (M ⁺ +1)
263	3-(8-(N-[methyl]aminocarbonyl)-[1,5]diazoperhydroonino-[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 469.2 (M ⁺ +1)

EXAMPLE 264

5 3-(6-(2-(methoxy)ethoxycarbonyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole

Stir 3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole (150 mgs, 0.38 mmol) and triethylamine (250 mgs, 2.4 mmol) in absolute methanol (20 mL). Add a solution of 2-bromoethylchloroformate (141 mgs, 0.75
10 mmol) in tetrahydrofuran (5 mL) slowly dropwise, then stir at 20°C for 1 hour. Add morpholine (2 mL, 22.9 mmol), reflux under nitrogen for 2 hours and concentrate under reduced pressure. Purify the product by preparative reverse phase high performance chromatography, followed by chromatography on a Varian® BondElut™ SCX column,

eluting with ammonia in methanol to obtain 115 mg (55%) of the title compound as an orange solid.

HRMS: $m/z = 555.2245$ (M+H)

5

EXAMPLE 265

3-(6-(2-(morpholin-4-yl)acetyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole hydrochloride

Add a solution of bromoacetyl chloride (0.185 gm, 1.17 mMol) in tetrahydrofuran (10 mL) slowly to a solution of 3-(5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole (0.15 gm, 0.38 mMol) and triethylamine (0.23 gm, 2.27 mMol) in absolute methanol (25 mL). Stir the resulting mixture for 1 hour at room temperature and then add morpholine (2 mL, 22.9 mMol). Heat at reflux for 2 hours, concentrate under reduced pressure, and subject to Varian® BondElut™ SCX chromatography, eluting with ammonia in methanol. Dissolve the desired product in 1 M hydrochloric acid and subject to preparative HPLC to provide the title compound as an orange solid (0.13 gm, 61%).

HRMS: 525.2113 (M+H)

EXAMPLE 266

3-(8-(cyanomethyl)-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole

Add bromoacetonitrile (0.1 g, 0.96 mmol) to a solution of 3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole dihydrochloride (0.2 g, 0.48 mol) in methanol (15 mL) and triethylamine (0.49 g, 4.8 mmol). Stir at 60°C overnight. Dilute the reaction mixture with saturated aqueous sodium bicarbonate, extract into ethyl acetate, and concentrate under reduced pressure. Purify by reverse phase preparatory chromatography, eluting with acetonitrile and water, and freeze-dry the pure fractions to provide the title compound as a red solid (0.050 g, 23%).

MS(ES): $m/z = 451.2$ (M⁺+1)

The compounds of EXAMPLES 267-271 are prepared essentially as described in EXAMPLE 266.

Example	Compound	Data
267	3-(6-((cyanomethyl)-6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole	MS(ES): m/z = 423.2 (M ⁺ +1)
268	3-(6-((carboxymethyl)-6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 442.2 (M ⁺ +1)
269	3-(6-((morpholin-4-yl)carbonylmethyl)-6,7-dihydro-6H-[1,4]diazepino[6,7,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 511.2 (M ⁺ +1)
270	3-(6-((morpholin-4-yl)carbonylmethyl)-5,6,7,8-tetrahydro-6H-[1,4]diazocino[7,8,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	HRMS: m/z = 525.2130 (M+H)
271	3-(8-((morpholin-4-yl)carbonylmethyl)-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 539 (M ⁺ +1)

EXAMPLE 273

- 5 3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(5-hydroxybenzofur-7-yl)-2,5-dioxopyrrole hydrochloride

Mix pyridine hydrochloride (5.4 g, 46.7 mmol) and 3-(8-(tert-butoxycarbonyl)-[1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(5-methoxybenzofur-7-yl)-2,5-dioxopyrrole (325 mg, 0.60 mmol). Heat and stir the mixture at 190-200°C under

10 nitrogen for 40 minutes. Cool to 25°C, dissolve in distilled water, and adjust to pH = 7.0 using aqueous 3 molar sodium carbonate. Extract the mixture with ethyl acetate. Combine the organic layers, wash with aqueous saturated sodium chloride, dry over anhydrous sodium sulfate, filter, and concentrate under reduced pressure.

- 15 Chromatograph on a reverse phase preparative high performance chromatography column, eluting with acetonitrile containing 0.01% hydrochloric acid to obtain the title compound as an orange solid (185 mg, 66%).

HRMS: 428.1610 (M+H)

The compounds of EXAMPLES 273-277 are prepared essentially as described in EXAMPLE 272.

Example	Compound	Data
273	3-([1,5]diazoperhydroonino[8,9,1-hi]indol-1-yl)-4-(4-hydroxybenzofur-7-yl)-2,5-dioxopyrrole hydrochloride	MS(ES): m/z = 428.0 (M ⁺ +1)
274	3-(6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(4-hydroxy-benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	HRMS: 400.1317 (M+H)
275	3-(6,7-dihydro-6H-[1,4]diazepino-[6,7,1-hi]indol-1-yl)-4-(5-hydroxy-benzofur-7-yl)-2,5-dioxopyrrole hydrochloride	HRMS: 400.1315 (M+H)
276	3-(5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)-4-(4-hydroxybenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 385.1201 (M+H)
277	3-(5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)-4-(5-hydroxybenzofur-7-yl)-2,5-dioxopyrrole	HRMS: 385.1203 (M+H)

EXAMPLE 278

5 3-(5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)-4-(4-(3-(diethylamino)propoxy)benzofur-7-yl)-2,5-dioxopyrrole
3-(5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)-4-(4-(3-(bromo)propoxy)benzofur-7-yl)-2,5-dioxopyrrole

10 Dissolve 3-(5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)-4-(4-(3-(hydroxy)propoxy)benzofur-7-yl)-2,5-dioxopyrrole (0.1 g, 0.232 mmol) in 10 mL dichloro-methane. Add carbon tetrabromide (0.077 g) and triphenyl-phosphine (0.061 g). Stir for 10 minutes and add another equivalent of both reagents. Stir 10 minutes then dilute with dichloromethane and wash with water followed by saturated aqueous sodium chloride. Dry over magnesium sulfate then filter and concentrate under reduced pressure.
15 Subject residue to silica gel chromatography, eluting with 2% methanol in dichloromethane to provide the desired compound (0.116g)
MS(ES): m/z = 506.2 (M+1)

Amination

20 Dissolve 3-(5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-1-yl)-4-(4-(3-(bromo)propoxy)benzofur-7-yl)-2,5-dioxopyrrole (0.058 g, 0.118 mmol) in 1.5 mL 1-methyl-2-pyrrolidinone and add diethylamine (2M in tetrahydrofuran, 0.3 mL) and heat to

60 °C for 16 hours. Partition between ethyl acetate and water and concentrate organic layer. Dissolve the residue in a minimal amount of methanol and load onto an SCX™ Varian column (pretreated with a 5% acetic acid: methanol solution). Wash column with methanol and ethyl acetate, and elute with 2M ammonia in methanol to provide the title compound.

MS(ES): 498.2 (M+1)

The compound of EXAMPLE 279 is prepared essentially as described in EXAMPLE 278.

Example	Compound	Data
279	3-(6-(tert-butoxycarbonyl)-6,7-dihydro-6H-[1,4]diazepino-[6,7,1-h]indol-1-yl)-4-(4-(3-(diethyl-amino)propoxy)benzofur-7-yl)-2,5-dioxopyrrole	MS(ES): m/z = 613.4 (M+1)

Kinase Inhibition Assay

The ability of the compounds of the present invention to inhibit the activity of the GSK-3β enzyme is measured according to a standard protocol (FIOL, Carol J., et al., A Secondary Phosphorylation of CREB³⁴¹ at Ser¹²⁹ Is Required for the cAMP-Mediated Control of Gene Expression: A Role for Glycogen Synthase Kinase-3 in the Control of Gene Expression, *J. Biol. Chem.*, **269**, 32187-32193 (1994)). Briefly, the catalysis of the reaction:



by GSK-3β is measured in a reaction mixture comprised of the following: 50 mM MOPS (4-morpholinepropanesulfonic acid) pH 7.0; 50 μM phosphoCREB peptide; 50 μM ATP; 0.5 μCi ATP[γ-³³P]; 12.5 mM MgCl₂; 0.03% Triton-X; 4% DMSO; and 1 nM recombinant human GSK-3beta. The reaction is initiated by the addition of enzyme. The final reaction volume is 100 μL. The reaction is allowed to proceed for 60 minutes at room temperature and is stopped by the addition of 75 μL of 10% phosphoric acid. To capture KRREIL⁽³³pS)RRP(pS)YR formed in the reaction and to remove unreacted AT³³P, 160 μL of the stopped reaction mixture is transferred to a pre-wetted (0.75% phosphoric acid) phosphocellulose microfiltration plate [Millipore Cat.# MAPH NOB 50]

and after 90 minutes incubation on the plate, the stopped reaction mixture is passed through the filter using a Titertek Map Extractor. The filter containing the trapped KRREIL(³³pS)RRP(pS)YR is washed with 220 µL of 0.75% phosphoric acid. Filter plates are blotted to remove droplets from the underdrain. The underdrain is removed from the filter and the filter is placed into a clear plate liner (Wallac, Inc.). Added to each well is 100 µL of Microscint 20 (Packard).

After standing at least six hours (preferably overnight), the plates are counted in a Trilux scintillation counter (Wallac, Inc.). The ability of a compound to inhibit GSK-3beta is determined by including various concentrations of the compound in the reaction mixture and comparing the signal produced to the signal produced in a reaction mixture without the compound.

The assay yields the molar concentration of the test compound that produces a 50% inhibition of the GSK-3beta enzyme activity (IC₅₀). The lower the value in this test, the more active the test compound is. The exemplified compounds exhibit IC₅₀ ≤ 0.2 µM.

Glycogen Synthesis Assay

The glycogen synthesis assay measures the increase in the production of glycogen both in the absence and in the presence of insulin in the cells. This test is done according to standard protocols. (Berger, J. and Hayes, N.S., Anal. Biochem., **261**, 159-163 (1998)). Briefly, 3T3-L1 adipocytes are plated and differentiated in a 96-well plate at 25,000 cells/well. The plate is serum-starved overnight. The serum-starvation media is removed just prior to assay, and the plate is washed with 100 µl/well Krebs-Ringer-Hepes buffer (KRBH). The KRBH is removed and 50 µl of compound (twice the amount of the final concentration) is added to the assay plate. Next, 50 µl of ¹⁴C-labeled glucose is added to the assay plate at 0.1 µCi/well. The plate is then incubated at 37°C for 2 hours.

The plate is washed with 100 µL/well of PBS, and the cells are lysed with 75 µl/well of 1N NaOH. The plate is heated at 70°C for 20 minutes. An aliquot (50 µl) of the supernatant is transferred from the assay plate to a Millipore FC filter plate containing 120 µl/well of ice-cold ethanol. The plate is allowed to stand for 2 hours at 4°C to facilitate precipitation. The ethanol is removed from the filter plate via a vacuum manifold, and the plate is washed with 100 uL/well of ice-cold 70% ethanol. The plate was allowed to dry overnight, and 75 µl/well of Microscint-20 was added to

the filter plate. The plate was then counted on a Packard Topcount. The compound of Example 114 was tested in this assay and increased glycogen synthesis by 3.7-fold at 0.1 μ M in the absence of insulin, and increased glycogen synthesis by 6.4-fold at 0.1 μ M in the presence of insulin.

5

Glucose Lowering Assay

The glucose lowering assay is an in vivo test that measures the effect of the test compound on blood glucose and triglycerides relative to insulin. (ELDAR-FINKLEMAN, H., et al., Expression and Characterization of Glycogen Synthase Kinase-3 Mutants and Their Effect on Glycogen Synthase Activity in Intact Cells, Proc. Nat. Acad. Sci., **93**, 10228-10233 (1996)). Briefly, ZDF rats (Charles River, Inc.) at six weeks of age are housed individually with free access to food and water. Rats are dosed with drug once daily by oral gavage, with the compound prepared as a suspension in 1% caboxymethylcellulose/0.25% Tween 80 (CMC-Tween). Vehicle controls are dosed with CMC-Tween only. The duration of study varied according to the protocol used, with acute dosing studies lasting one day and dose escalation studies lasting seven days. Body weights and food consumption measurements are also performed once a week for seven-day studies. For measurement of blood glucose and triglycerides, blood samples of 600 μ l are collected by the tail snip method. (The tail snip for blood sampling is as follows: 1-2 mm of the tail is snipped with a sharp blade. After collection of blood, a scab forms at the site of wound. This scab is removed and the tail is gently massaged for other subsequent bleedings.) Glucose and triglyceride determinations are performed on a Hitachi 912 metabolic analyzer, with a kit utilizing the Trinder method. On termination of study, specific tissues (e.g., heart, pancreas, adipose tissues, and liver) are excised to evaluate the effect of these drugs on their metabolic functions. The compound of Example 114 was tested in this assay and lowered glucose by 56% at a dose of 10 mg/kg.

Ex Vivo Brain Assay

The ex vivo brain assay assesses the GSK-3 β kinase activity of the test compound in brain cortex tissue according to standard protocols (Wang, *et al.*, Anal. Biochem., **220**, 397-402 (1994)).

5 The ex vivo GSK-3 β kinase activity of a compound is assayed following oral dosing of 2 to 3 month old PDAPP or CD-1 mice. After a 20 mg/kg, 24-hour dose, followed by an additional three-hour dose, brain cortex tissue is dissected and homogenized in freshly prepared lysis buffer (10 mM K₂HPO₄ pH 7.2, 1 mM EDTA, 5 mM EGTA, 10 mM MgCl₂, 50 mM β -Glycerophosphate, 1 mM Na₃VO₄, 2 mM DTT, 1
10 μ M Microcystin, COMPLETE protease inhibitor tablet, no detergent). Following a thirty-minute incubation on ice, cortex homogenate samples are centrifuged (100,000 G) for 30 minutes at 4°C (Ahmed, N.N., *et al.*, Oncogene, **8**, 1957 (1983)). The total protein concentration of homogenate is determined using the BCA method (Pierce). GSK-3 β activity in cytosolic homogenate from vehicle- and compound-treated mice is then
15 assayed. The kinase reaction occurs in a 50 μ l total volume containing 20 mM MOPS pH 7.4, 25 mM β -glycerol phosphate, 5 mM EGTA, 1 mM NA₃VO₄, 1 mM DTT, 15 mM MgCl₂, 100 μ M cold ATP, 200 μ M CREB peptide, 10 μ L cytosolic cortex brain homogenate, and 5 μ Ci γ -³³P-ATP. The reactions are incubated for thirty minutes at 30°C using a Costar round-96 polypropylene plate. Reactions are then stopped with the
20 addition of 10% H₃PO₄ and transferred to a Millipore MAPH-NOB 96-well phosphocellulose plate. Next, the reaction is incubated at room temperature for 1.5 hours, filtered and washed with 320 μ l 0.75% H₃PO₄, and filtered and washed with 160 μ l H₃PO₄ at the same concentration using a vacuum manifold. The filter plate is then placed in a carrier plate, and 100 μ l of Microscint 20 is added to each well. The plate is sealed
25 with sealing tape and incubated overnight at room temperature. The following day, the filter plate is read for ³³P on Top Count (Packard). Finally, CPM is normalized to CPM per μ g of total protein. The compound of Example 114 was tested in this assay and inhibited kinase activity by 30% at a dose of 20 mg/kg.

Beta-Catenin Protection Assay

30 The beta-catenin assay is the fold induction over basal beta-catenin and is performed according to standard protocols (Hedgepeth, C.M., Dev. Biol., **185**, 82-91

(1997); Chen, G., *et al.*, *J. Neurochem.*, **72**, 1327-1330 (1999); Hong, M., *et al.*, *J. Biol. Chem.*, **272**, 25326-25332 (1997)).

The human familial Alzheimer's disease (FAD) presenilin-1 AG04160C lymphoblast cell line (Coriell Cell Repository, Camden, NJ) is maintained as a suspension culture in RPMI 1640 (with L-Glutamine) supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin in an atmosphere of 37°C and 5% CO₂. The AG04160C FAD lymphoblast cells are seeded in T-25 cm² flasks at 2.5 to 5.0 X10⁵ cells/ml in a total volume of 10 ml. Following 16-18 hours of growth, cells are treated with compound at concentrations of 0.1 µM, 1.0 µM, and 10 µM, and are incubated for an additional 24 hours. At the completion of the 24-hour incubation, cells are harvested, washed with PBS, and lysed in freshly prepared lysis buffer (10 mM K₂HPO₄ pH 7.2, 1 mM EDTA, 5 mM EGTA, 10 mM MgCl₂, 50 mM β-Glycerophosphate, 1 mM Na₃VO₄, 2 mM DTT, 1 µM Microcystin, 1 mM PMSF, 10 µg/ml leupeptin, 1 µg/ml pepstatin, 1 µg/ml aprotinin, 1% Triton X-100). After a thirty-minute incubation on ice, cells are centrifuged (14,000 rpm) for 30 minutes at 4°C, and resulting supernatants are used as whole cell lysates. The total protein concentration in whole cell lysate samples is determined using the BCA method (Pierce). Next, 15 µg of sample is loaded on a 10% Bis-Tris NuPage gel and transferred to a pure nitrocellulose membrane followed by β-catenin immunoblot analysis using a β-catenin specific antibody (Transduction Labs). The β-catenin accumulation/stability is then quantified following densitometry analysis of protein bands (Kodak Digital Science). Final results are reported as fold induction over basal β-catenin. The compound of Example 114 was tested in this assay and induced a 9.8-fold induction of β-catenin at 0.1 µM.

Oral administration of the compounds of the present invention is preferred. However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine, and the intravenous route may be preferred as a matter of convenience or to avoid potential complications related to oral administration. Compounds of Formula I may also be administered by the percutaneous, intramuscular, intranasal or intrarectal route in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs, the convenience

of the patient and the caregiver, and other relevant circumstances (Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)).

The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material that can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solutions, suspensions, or the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations of the present invention may be determined by methods well known to the skilled artisan.

The tablets, pills, capsules, troches, and the like may also contain one or more of the following adjuvants: binders such as povidone, hydroxypropyl cellulose, microcrystalline cellulose, or gelatin; excipients or diluents such as: starch, lactose, microcrystalline cellulose or dicalcium phosphate, disintegrating agents such as: croscarmellose, crospovidone, sodium starch glycolate, corn starch and the like; lubricants such as: magnesium stearate, steric acid, talc or hydrogenated vegetable oil; glidants such as colloidal silicon dioxide; wetting agents such as: sodium lauryl sulfate and polysorbate 80; and sweetening agents such as: sucrose, aspartame or saccharin may be added or a flavoring agent such as: peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials that modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, hydroxypropyl

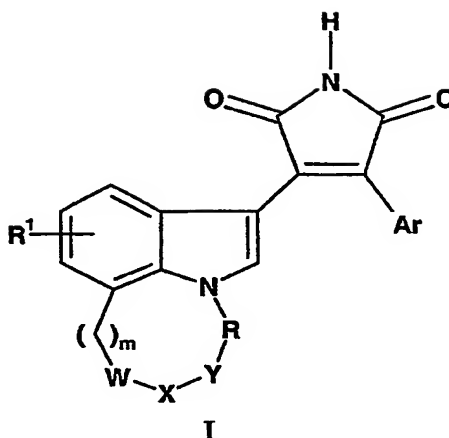
methylcellulose, polymethacrylates, or other coating agents. Syrups may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

5 The compounds of Formula I are generally effective over a wide dosage range.

For example, dosages per day normally fall within the range of about 0.0001 to about 30 mg/kg of body weight. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, and therefore the above
10 dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity
15 of the patient's symptoms.

WE CLAIM:

1. A compound of Formula I:



where:

5 R^1 is hydrogen, halo, C_1 - C_4 alkyl, or C_1 - C_4 alkoxy;

m is 0, 1, 2, 3, or 4;

R is $-(CH_2)_n-$ or $-CH(OH)-CH(OH)-CH_2-$;

n is 0, 1, 2, 3, or 4;

$W-X-Y$ is $-CH_2-CH_2-CH_2-$, $-CH(R^3)-N(R^2)-CH(R^3)-$, or $-CH(R^3)-N(R^4)-C(O)-$;

10 R^2 is hydrogen, $-(C_1-C_4 \text{ alkylene})-R^5$, C_5-C_7 cycloalkyl, tetrahydropyran-4-yl, $-C(O)R^6$, $-CO_2R^7$, $-CO(NR^8R^9)$, $-SO_2NH_2$, $-SO_2(C_1-C_4 \text{ alkyl})$, or an amino acid residue;

R^3 and $R^{3'}$ are independently selected from the group consisting of hydrogen and C_1 - C_4 alkyl provided that only one of R^3 and $R^{3'}$ may be C_1 - C_4 alkyl;

R^4 is hydrogen or C_1 - C_4 alkyl;

15 R^5 is hydrogen, cyano, phenyl, imidazol-2-yl, $-COOH$, or $-(\text{morpholin-4-yl})\text{carbonyl}$;

R^6 is hydrogen, C_1 - C_{10} alkyl, pyridinyl, pyrazinyl, morpholin-4-yl, piperazinyl, 1- $(C_1-C_4 \text{ alkyl})$ piperazin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl, 1- $(C_1-C_4 \text{ alkoxy-carbonyl})$ piperidin-4-yl, or $-CH_2-R^{10}$;

20 R^7 is C_1 - C_6 alkyl, 2-methoxyethyl-1-yl, $-(C_1-C_2 \text{ alkylene})\text{morpholin-4-yl}$, or phenyl optionally substituted with one or two substituents independently selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, and trifluoromethyl;

R^8 is hydrogen or C_1 - C_4 alkyl;

R^9 is hydrogen or C_1 - C_4 alkyl;

R^{10} is $-OCH_2CH_2OCH_3$, $-NR^{14}R^{15}$, or morpholin-4-yl;

Ar is benzofur-4-yl, benzofur-7-yl, benzothien-4-yl, benzothien-7-yl, 1-(R^{11})benzimidazol-4-yl, 1-(R^{11})indol-4-yl, indol-7-yl, isoquinolin-5-yl, 2,3-dihydrobenzofur-4-yl, 2,3-dihydrobenzofur-7-yl, 1,3-dihydroisobenzofur-4-yl, 1,3-dihydroisobenzofur-5-yl, benzo[1,3]dioxol-4-yl, benzo[1,3]dioxol-5-yl, 2,3-dihydrobenzo[1,4]dioxin-5-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2',2'-difluorobenzo[1,3]dioxol-4-yl, or 2',2'-difluorobenzo[1,3]dioxol-5-yl each optionally substituted in the phenyl ring with substituents R^{12} and R^{13} , or Ar is a group selected from imidazo[1,2-*a*]pyridin-3-yl optionally substituted with cyano, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-3-yl, imidazo[1,2-*a*]pyridin-5-yl, furo[3,2-*c*]pyridin-7-yl optionally substituted with halo or $-NR^{14}R^{15}$, thieno[3,2-*b*]pyridin-7-yl, or pyrazolo[2,3-*a*]pyridin-3-yl;

R^{11} is hydrogen, C_1 - C_4 alkyl, or $-(CH_2)_p-G$;

R^{12} is halo, hydroxy, amino, C_1 - C_4 alkoxy, $-NHC(O)(C_1-C_4 \text{ alkyl})$, or $-O-(CH_2)_p-G$;

R^{13} is halo;

p is 2, 3, 4, or 5;

G is hydroxy or $NR^{14}R^{15}$;

R^{14} and R^{15} are independently selected from the group consisting of hydrogen and C_1 - C_5 alkyl; or a pharmaceutically acceptable salt thereof, provided that when n is 0, W-X-Y is not $-CH(R^{3'})-N(R^2)-C(O)-$.

2. A compound of Claim 1 where Ar is benzofur-4-yl, benzofur-7-yl, or 2,3-dihydrobenzofur-7-yl optionally substituted in the phenyl ring with substituents R^{12} and R^{13} .

3. A compound of Claim 2 where R^{12} is fluoro, hydroxy, methoxy, or $-NHC(O)CH_3$.

4. A compound of either of Claims 2 or 3 where Ar is benzofur-7-yl.

5. A compound of Claim 1 where Ar is imidazo[1,2-*a*]pyridin-3-yl, imidazo[1,2-*a*]pyridin-5-yl, or furo[3,2-*c*]pyridin-7-yl.

6. A pharmaceutical formulation comprising a compound of any of Claims 1-5 in
5 combination with a pharmaceutically acceptable carrier, diluent or excipient.

7. A method of treating diabetes in a mammal comprising administering to a
mammal in need of such treatment an effective amount of a compound of any of Claims
1-5.

8. A method of treating Alzheimer's disease in a mammal comprising
administering to a mammal in need of such treatment an effective amount of any of
Claims 1-5.

9. A method of inhibiting GSK-3 in a mammal comprising administering to a
mammal in need of such treatment a GSK-3 inhibiting amount of a compound of any of
Claims 1-5.

ABSTRACT

The present invention provides kinase inhibitors of Formula I:

